

Department of Mechanical Engineering

University of Canterbury
Te Whare Wānanga o Waitaha
Private Bag 4800
Christchurch 8020, New Zealand

Telephone: 64-3-366 7001
Facsimile: 64-3-364 2078
Website: www.mech.canterbury.ac.nz



ME Research Thesis

Randomised Controlled Trial Initialisation and Management in the Intensive Care Unit

Student: Vincent John Major
Senior Supervisor: Dist. Prof. J Geoffrey Chase
Co-Supervisor: Dr. Yeong Shiong Chiew
Enrollment Date: 01 March 2015
Submission Date: 11 November 2015

Table of Contents

TABLE OF CONTENTS	2
1.0 INTRODUCTION	6
1.1 MOTIVATION	6
1.2 FUNDAMENTAL BACKGROUND	7
1.2.1 CONTEXT	8
1.2.2 FUNDAMENTALS	9
1.3 RESEARCH OBJECTIVES	11
2.0 REVIEW OF MECHANICAL VENTILATION	12
INTRODUCTION	12
2.1 MV PARAMETERS, MEASUREMENTS AND MODES	13
2.1.1 BREATH PARAMETERS – EVERY BREATH HAS THESE	13
Tidal volume	13
Driving Pressure	14
2.1.2 MV INPUT SETTINGS	14
2.1.3 MV MODES	15
2.1.4 MV OUTCOME MEASUREMENTS	16
2.1.5 SUMMARY:	17
2.2 THE PROBLEMS WITH MV MANAGEMENT	17
2.2.1 EFFECT OF EXCESSIVE PRESSURE – BAROTRAUMA	18
2.2.2 EFFECT OF EXCESSIVE VOLUME – VOLUTRAUMA	18
2.2.3 EFFECT OF TOO LITTLE VOLUME AND/OR PRESSURE – ATELECTRAUMA	18
2.2.4 BIOTRAUMA AND OTHER ADVERSE EFFECTS RELATED TO SUB-OPTIMAL MV SETTINGS	19
2.2.5 ARDS DIAGNOSIS AS A RATIO OF BLOOD OXYGENATION TO INSPIRED OXYGEN AND OTHER FACTORS	19
2.2.6 THE PROBLEM WITH PATIENTS – HETEROGENEITY IN AFFECTED LUNG AND RESPONSE	21
Inter-patient variability in heterogeneity of disease and response	22
Intra-patient variability 1: in evolution of disease over time (need for real-time vs intermittent)	22
Intra-patient variability 2: heterogeneity of the lung in ARDS or response to MV in respiratory failure	22
2.2.7 SUMMARY:	22
2.3 MV STRATEGIES AND TRIALS: TO OVERCOME THESE ISSUES	23

2.3.1	LUNG RECRUITMENT STRATEGIES: RECRUITMENT MANOEUVRES	23
2.3.2	COMPLIANCE STRATEGIES	24
2.3.3	LUNG PROTECTIVE STRATEGIES	25
	ARDSNet:	25
	OLA:	26
2.3.4	VARIABLE VENTILATION STRATEGIES	27
2.3.5	HIGH FREQUENCY OSCILLATION (HFO) AND AIRWAY PRESSURE RELEASE VENTILATION (APRV) STRATEGIES	28
2.3.6	TRANSPULMONARY PRESSURE AND OESOPHAGEAL PRESSURE PEEP TITRATION	29
2.3.7	SUMMARY	29
2.4	THE REAL NEEDS HIGHLIGHTED	30
2.4.1	MANAGING INTRA-PATIENT VARIABILITY → REAL-TIME, BREATH-TO-BREATH	30
2.4.2	MANAGING INTER- AND INTRA- PATIENT VARIABILITY USING A MEASURABLE METRIC FOR PATIENT-SPECIFIC TITRATION → MINIMISING RESPIRATORY ELASTANCE	30
2.4.3	RECRUIT THE LUNG AND ASSESS PATIENT-SPECIFIC RESPONSE TO PRESSURE → USE OF REGULAR RM	30
2.5	THE NEED OF MODEL-BASED MECHANICAL VENTILATION	31
2.5.1	MODELS AND BACKGROUND	31
2.5.2	MINIMUM VS INFLECTION ELASTANCE	32
2.5.3	PEEP SELECTION VIA REGULAR RM	32
2.6	CHAPTER SUMMARY:	33
3.0	<u>MODEL-BASED MECHANICAL VENTILATION: APPLICATION IN A CLINICAL SETTING IN REAL-TIME</u>	34
3.1	MODEL-BASED VENTILATION THEORY	34
3.1.1	PILOT TRIALS	34
3.1.2	SINGLE-COMPARTMENT MODEL AND PHYSIOLOGY	35
	The Single-Compartment Model	35
3.2	THE EARLY PLAN AND PRIMARY GOAL FOR HARDWARE	39
3.3	COMPUTER REQUIREMENTS TO OPERATE CURE SOFT	39
3.4	HARDWARE SPECIFICATIONS	40
3.5	COMPUTING AND DISPLAY HARDWARE CHOICES	42
3.6	SELECTING A TABLET PC AND MINI PC FOR TESTING	44
3.6.1	TABLET PC	44
3.6.2	NUC MINI PC.	44
3.6.3	HEAT TESTING OF MICROSOFT SURFACE PRO VERSUS NUC.	45

3.7	MONITOR SELECTION	47
3.7.1	TOUCH MODE	47
3.7.2	SPECIFIC CONCERNS IN AN ICU ENVIRONMENT	48
3.7.3	MONITOR OPTIONS CONSIDERED	48
3.7.4	SELECTING THE MONITOR	50
3.8	MOUNTING THE COMPUTING HARDWARE	50
3.8.1	MOUNTING CONCEPT AND KEY FACTORS	50
3.8.2	COMMERCIALLY AVAILABLE MOUNTS	51
3.8.3	SIMPLE CUSTOM MOUNTING SYSTEMS	51
3.8.4	PROTOTYPE MOUNTING DESIGN	55
3.8.5	LOADING PATHS	56
3.8.6	PROTOTYPE MANUFACTURE	57
3.8.7	PROTOTYPE TESTING	57
3.9	FINAL MOUNT DESIGN	58
3.9.1	DETAILED CALCULATIONS.	58
3.9.2	PROCUREMENT COSTS	59
3.9.3	FINAL ENGINEERING DRAWINGS	59
3.10	CHAPTER SUMMARY:	60
4.0	RETROSPECTIVE ANALYSIS OF ICU PATIENT DATA	61
4.1	DETERMINING THE REQUIRED NUMBER OF HARDWARE UNITS	61
4.1.1	INTRODUCTION	61
4.1.2	METHODS	62
4.1.3	RESULTS AND DISCUSSION	63
4.1.4.1	Limitations and recommendations	67
4.1.5	SUMMARY: UTILITY ANALYSIS	67
4.2	ICU DIAGNOSTIC CODES AND ESTIMATED RISK OF DEATH METRICS	68
4.2.1	INTRODUCTION	68
4.2.2	METHODS	68
4.2.3	RESULTS	69
4.2.3.1	Diagnostic code groups	70
4.2.3.2	Diagnostic code subgroups	73
4.2.3.3	Limitations	75
4.2.4	SUMMARY: ROD ANALYSIS	76
4.3	RETROSPECTIVE ANALYSIS OF ICU READMISSIONS	76

4.3.1	INTRODUCTION	76
4.3.2	METHODS	76
4.3.3	RESULTS AND DISCUSSION	77
4.3.3.1	Complete ICU cohort of 5176	77
4.3.3.2	Refined CURE RCT Eligible cohort of 645	82
4.3.3.3	Limitations	84
4.3.4	SUMMARY: READMISSION ANALYSIS	84
4.4	CHAPTER SUMMARY:	85
5.0	TRIAL COMMENCEMENT	86
5.1	PRE TRIAL COMMENCEMENT	86
	CURE RCT Manual	86
5.2	CURE RCT WORK-FLOW	86
5.3	DATA COLLECTION AND REPOSITORY	89
5.4	CURE SOFTWARE AMENDMENTS	89
5.5	CHAPTER SUMMARY:	93
6.0	CHALLENGES AND FUTURE WORK	94
6.1	CHALLENGES FACED	94
6.1.1	HARDWARE INTO THE ICU	94
6.1.2	INTENSIVIST CONSENSUS	94
6.2	FUTURE WORK	94
6.2.1	PRELIMINARY ANALYSES	95
6.2.2	VIRTUAL PATIENTS	95
6.2.3	IMPROVED SIGNAL PROCESSING	95
6.3	CHAPTER SUMMARY:	96
7.0	CONCLUSIONS	97
8.0	REFERENCES	99

1.0 Introduction

Collaboration between the University of Canterbury's Centre for Bioengineering and the Christchurch Hospital Intensive Care Unit (ICU) has been occurring for over 15 years. Recently, one focus of research has been improving the delivery of mechanical ventilation (MV) therapy, an essential life-support restricted to the ICU. The severely ill ICU patients commonly have a secondary diagnosis of acute respiratory failure, acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). These three terms are not diagnosable by a specific pathogenesis responsible for each disease but instead, are syndromes classified by specialists to include respiratory failure or distress caused by any primary diagnosis.

Since each patient has an incomparable disease state, a cohort of respiratory failure patients is extremely heterogeneous. Research has shown that the entire lung is not affected evenly by disease and each patient's lungs are also heterogeneous. The significant inter- and intra-patient variability makes both diagnosis and treatment of ALI or ARDS difficult to standardize. Each patient should be treated as an individual with care chosen for their specific lung condition at that time.

1.1 Motivation

The current standard of MV therapy in the ICU relies heavily on either clinician experience and intuition or a generalised approach such as recommended in large randomised controlled trial such as ARDSNet, EXPRESS, ALVEOLI or LOVS trials (The ARDS Network, 2000; Brower et al., 2004; Meade et al., 2008; Mercat et al., 2008; Briel et al., 2010). These generalised approaches target improved outcomes for the cohort while disregarding the plethora of information easily available about the individual patient's condition. Thus, a method to guide patient-specific MV therapy is needed to improve individual patient outcomes.

Internationally, there is a trend towards individualised care but MV therapy is effectively the same now as it was in the 1990s (Slutsky, 1993). The ventilator machines are more precise in data acquisition and can provide more information to the clinicians at the bedside. However, the principal strategies of MV therapy remain unchanged throughout the years. Specifically,

there exists relatively few non-invasive monitoring tools that are financially and clinically feasible (thus excluding current electrical impedance tomography [EIT] (Fagerberg et al., 2009) and computed tomography [CT] (Slutsky and Hudson, 2006; Brenner and Hall, 2007; Chase et al., 2014; Sundaresan and Chase, 2011)) to monitor a patient's breath-to-breath lung condition in real-time that could be used to guide MV therapy. Thus, there is a need for a method that can monitor patient-specific condition in real-time without compromising patients' care and without added clinical protocol burden.

Positive end-expiratory pressure (PEEP) is one of the primary mechanical ventilation settings, that is widely used to improve MV patients breathing (Slutsky and Hudson, 2006; Rouby et al., 2002; Sundaresan and Chase, 2011). Studies in experimental animal trials proposed that setting PEEP to where the lung had minimal elastance (or maximum compliance) would be clinically beneficial (Suter et al., 1975; Carvalho et al., 2007; Lambermont et al., 2008; Chiew et al., 2011; Pintado et al., 2013). At this point, the lung has expanded where the greatest volume is achieved without overstretching the lung tissue that can cause further lung injury. This minimal-elastance PEEP concept can be achieved using a model-based approach to estimate the respiratory elastance in real-time without additional invasive measuring tools.

Aside from animal trials, clinical trials including pilot trials conducted by researchers from University of Canterbury (UC) and the Christchurch Hospital ICU have shown great promise in minimal-elastance PEEP selection (Chiew et al., 2011; Chiew et al., 2015c). To proceed with proving the efficacy of model-based ventilation to improve patient care, a randomised controlled trial (RCT) is required to compare model-based ventilation to the current standard of care in a clinical setting. RCT is regarded as the gold-standard proof of the effectiveness of a treatment in the medical community (Akobeng, 2005). This planned RCT with collaboration with Christchurch Hospital is called the Clinical Utilisation of Respiratory Elastance randomised controlled trial (CURE RCT).

1.2 Fundamental Background

The following fundamental background aims to briefly introduce key information related to both model-based ventilation before the Chapter 2.0 – Literature Review.

1.2.1 Context

MV is a core support for patients in the ICU affecting up to 50% of ICU patients (≈ 800 patients per year in Christchurch and 8000 per year in New Zealand) with a considerable associated cost (Esteban et al., 2000; Dasta et al., 2005; ANZICS, 2010) approximated near \$1800 per patient per day. The primary objective of MV is to support the breathing of patients with respiratory failure (such as acute lung injury [ALI] or acute respiratory distress syndrome [ARDS]). The incidence of ARDS has been reported at 31 per 100,000 per year and may account for 36,000 deaths per year in a country the size of the US (Schoenfeld et al., 2002). The mortality rate from ALI or ARDS is approximately 40 to 50% (The ARDS Network, 2000) and long-term survivors experience serious morbidity (Meade et al., 2008). MV supports respiratory failure by increasing airway pressure to maximise recruitment (the proportion of open lung units) to encourage gas-exchange and enable recovery without damaging healthy lung units (Mertens et al., 2009). However, while there is agreement that lower tidal volumes are preferred (The ARDS Network, 2000; Girard and Bernard, 2007; The ART Investigators, 2012), there are no guidelines (and many conflicting trial results (Amato et al., 1998; Brower et al., 2004; Meade et al., 2008; Mercat et al., 2008; Oba et al., 2009; Briel et al., 2010), many of which have failed to reach statistical significance) for optimising the level of added pressure or PEEP. Typically, lower PEEP is considered better (Hickling et al., 1990; Gattinoni et al., 2010), but can lead to increased cases of oxygen desaturation and hypoxemia (examples of MV failures) (Brower et al., 2004; Guerin, 2011). The result is a difficult problem of balancing the benefits of added pressure with the associated risks. As current tools and methods cannot provide insight into patient-specific response to PEEP (Sundaresan and Chase, 2011), the best approach to set MV remains uncertain.

As a result, patient care can be variable and costly (Dasta et al., 2005), affecting patient-centered quality of care and clinical outcomes (Chase et al., 2011). In particular, ventilated patients stay 70% longer in ICU and cost 140% more (Dasta et al., 2005) than non-MV patients, indicating the potential for improving care. The main problem is that the lung of a patient with ALI or ARDS is very heterogeneous with significant inter- and intra-patient variability. Thus, what works for one patient may lead to ventilator induced lung injury (VILI) in another (Chiew et al., 2011; Thammanomai et al., 2013). The current standard of care is to perform an invasive recruitment manoeuvre to determine how best to titrate care (Malbouisson et al., 2001; Borges et al., 2006; Fan et al., 2008; de Matos et al., 2012). Thus, optimising MV management requires a means of assessing patient-specific lung condition

and patient-specific response to MV therapy using a model-based approach, to account for these variabilities and optimise treatment without excessive clinical effort or recruitment manoeuvres (RMs).

Recently, several new model-based metrics for assessing patient-specific lung elastance (Chiew et al., 2011; Chiew et al., 2012; Chiew et al., 2015c), recruitment (Sundaresan et al., 2009; Sundaresan and Chase, 2011), and lung volume response to MV (Sundaresan et al., 2011b) have been developed. Importantly, they all offer insight into patient-specific condition that is not available via typical static surrogate estimates (Lucangelo et al., 2007; Brochard et al., 2012), and, equally, they can be estimated breath-to-breath, and monitored as a surrogate of patient condition, as well as potentially being used to guide therapy (Chiew et al., 2011; Sundaresan et al., 2011a). These models all offer the potential to guide MV therapy choices, have all been individually clinically validated, but have not yet been used to prospectively guide therapy directly (Chiew et al., 2011; Sundaresan et al., 2011a). The upcoming CURE RCT seeks to prove their potential in direct clinical use.

1.2.2 Fundamentals

The pathogenesis of ALI or ARDS involves pulmonary edema, diffuse cellular destruction, lesions at the alveolar-capillary interface, alterations in permeability, alveolar collapse and disordered repair (Amato et al., 1998; Meade et al., 2008). However, the aetiology of ALI/ARDS is dependent on the patient's primary diagnosis and is thus patient-specific.

Although MV provides an essential life support, it can also degrade lung condition through regional overdistension, atelectrauma and oxygen toxicity (Slutsky, 1999). Results of the ARDSNet study (The ARDS Network, 2000) is the standard for current comparative trials. Experimental work has reported that atelectrauma is common in patients diagnosed with ARDS and may be more significant in ARDS mortality than originally thought (Meade et al., 2008). Atelectrauma can be mitigated by attempting to open collapsed lung tissue with RMs and ventilating with high PEEP levels to prevent (re)collapse (Meade et al., 2008). Meade et al. (Meade et al., 2008) have proposed that MV strategies that combine low tidal volumes with RMs and high PEEP to prevent atelectrauma would be ideal for lung protection.

PEEP is known to reduce hypoxemia and intrapulmonary shunting in ARDS patients and the clinical practice of titrating PEEP ameliorates these effects (Mercat et al., 2008). PEEP-induced alveolar recruitment helps to avoid airway collapse and reopening, protects lung

surfactant and improves ventilation homogeneity within the lung (Mercat et al., 2008). Although alveolar recruitment and oxygenation are often related, oxygenation is complex and affected by many factors and therefore should not be used as a surrogate for recruitment (Mercat et al., 2008).

The heterogeneity of ALI/ARDS and the complex distribution of pressures within the lung means that even at low PEEP some healthy lung units may be over stretched and at high PEEP some unhealthy lung units may remain collapsed (Chiew et al., 2011). Repeated opening and closing of small airways may be prevented by higher PEEP settings (The ARDS Network, 2000; Amato et al., 1998). Both insufficient and excessive PEEP during MV has adverse effects on patient condition and recovery (Rouby et al., 2002; Treggiari et al., 2002; Brower et al., 2004).

Normal subjects at rest inhale 7 to 8 mL/kg (The ARDS Network, 2000), the use of lower tidal volumes may reduce lung stretch and thus VILI. MV therapy using low tidal volumes is generally accepted to improve patient care and reduce mortality. In particular, work reported by The ARDS Network (2000) comparing a traditional approach, using 12 mL/kg, to a low tidal volume approach using 6 mL/kg reported a reduction in mortality from 39.8% to 31.0% ($p = 0.007$, $n=861$).

The use of low tidal volumes and plateau pressure no more than 30 cmH₂O was reported to increase survival among ARDS patients (The Acute Respiratory Distress Syndrome Network, 2000). Limiting hyperinflation has become a primary objective of MV setting selection, since PEEP may increase hyperinflation, a compromise must be found between the improved recruitment and overdistension (Mercat et al., 2008).

The patient's unconscious attempts to breath despite being ventilated can disrupt estimation of respiratory elastance. Muscular efforts can increase or decrease the volume and pressure within the lung which is not included in most models. (The only ventilation mode to monitor muscular efforts is neurally adjusted ventilatory assist [NAVA] which is inherently invasive). The use, or overuse, of muscle relaxants to reduce the patient's attempts to breathe may be clinically undesirable (Chiew et al., 2015c). However, recent work by Pintado et al. (Pintado et al., 2013) suggests that maximum compliance (minimum elastance) can be difficult to observe in some patients and muscle relaxants are necessary.

As PEEP increases from zero, respiratory elastance drops – as lung volume is easily recruitable at low pressures, volume is recruited faster than the lung pressure increases (Carvalho et al., 2007; Suarez-Sipmann et al., 2007; Meade et al., 2008; Chiew et al., 2011; Chiew et al., 2015c). At some PEEP, little or no additional lung volume is recruited with added PEEP and the elastance begins to rise, the lung is beginning to stretch (Chiew et al., 2015c; Chiew et al., 2011). However, the elastance curve does not always depict a clear minimum elastance, in such cases the precautionous selection of inflection-elastance can represent a ‘safer’ approach (Chiew et al., 2011).

1.3 Research Objectives

This research focuses on design and development of a randomised controlled trial to investigate the efficacy and effectiveness of a model-based mechanical ventilation treatment compared to a standard treatment. Specifically, prior to commencement of the RCT, preparations must be made to ensure that the clinical protocol is safe, ethical and suitable to address the research hypothesis; that the paperwork and data collected will be managed efficiently and stored appropriately; that the intrusion to both the clinicians and the patients of additional work or equipment in the bed-space will be minimal but justified; and the technicians, nurses, registrars, and intensivists are all on-board regarding the need for the trial, are trained regarding the clinical protocol and use of the software, and are willing to assist the trial.

A summary of the thesis chapters are as shown below:

- Chapter 2 contains a literature review in the form of a draft review article that presents the clinical background and motivation for a model-based respiratory mechanics RCT.
- Chapter 3 presents the process of hardware development in preparation for the RCT.
- Chapter 4 introduces three retrospective analysis using past ICU data used to help plan for study commencement.
- Chapter 5 presents the process of preparing the documentation, clinical protocol and study plan before the RCT can begin.
- Chapter 6 describes the challenges faced during this research and the avenues for future work.

2.0 Review of Mechanical Ventilation

Introduction

Mechanical ventilation (MV) supports respiratory failure patients by increasing airway pressure to maximise recruitment and providing flow to reduce the work of breathing, thus promoting improved gas-exchange and enabling recovery. In particular, the goal is to do so without further damaging healthy lung units (Mertens et al., 2009), while alleviating the patient's respiratory effort. However, while there is agreement that lower tidal volumes are preferred (The ARDS Network, 2000; Girard and Bernard, 2007), there are few specific guidelines and many conflicting trial results (Amato et al., 1998; Brower et al., 2004; Villar et al., 2006; Meade et al., 2008; Mercat et al., 2008; Oba et al., 2009; Briel et al., 2010) that can be used to optimise the level of positive end-expiratory pressure (PEEP) (Oba et al., 2009). Hence, current approaches tend to prefer low tidal volumes in conjunction with either recruitment manoeuvres (RMs) or moderate PEEP to keep the lung open (Thammanomai et al., 2013).

Although MV provides essential life support, it can also degrade lung condition through regional overdistension, atelectrauma, oxygen toxicity, and triggering alveolar and systematic inflammatory responses (Slutsky, 1999; Rose, 2010). Traditionally, lower PEEP was considered superior (Hickling et al., 1990; Gattinoni et al., 2010). However, lower PEEP can lead to increased cases of oxygen desaturation and hypoxemia (Brower et al., 2004; Guerin, 2011) and worsened lung injury indicated by a greater number of rescue therapies and death after rescue therapy (Briel et al., 2010).

In contrast, higher PEEP is known to reduce hypoxemia (Meade et al., 2008; Rouby et al., 2002) by improving gas exchange (Oba et al., 2009) and oxygenation (Brower et al., 2004; Borges et al., 2006; de Matos et al., 2012). Other benefits include increasing recruitment (Malbouisson et al., 2001; Borges et al., 2006; de Matos et al., 2012), stabilising injured or collapsed alveoli (Thammanomai et al., 2013; Rouby et al., 2002) to reduce further injury or VILI (Brower et al., 2004; Briel et al., 2010), reducing inflammatory mediators in plasma and bronchoalveolar lavage fluid (Ranieri et al., 1999), and improving ventilation homogeneity within the ARDS lung (Mercat et al., 2008). It has been hypothesized that MV strategies that combine low tidal volumes with RMs and higher PEEP to prevent atelectrauma would be ideal for lung protection (Meade et al., 2008; Rose, 2010).

However, the optimal level of PEEP is patient-specific and not easily titrated. The current standard of care is to perform an invasive recruitment manoeuvre (RM) to determine how best to titrate care (Borges et al., 2006; Fan et al., 2008; de Matos et al., 2012), but the specifics of the best RM for this task remains debatable (Fan et al., 2008; Guerin, 2011; Chiew et al., 2015c). As current tools and methods cannot provide enough insight into patient-specific response to PEEP (Sundaresan and Chase, 2011), particularly breath-to-breath or hour-to-hour, the best approach to PEEP selection remains uncertain (Sundaresan and Chase, 2011; Chiew et al., 2015c; Rose, 2010; Thammanomai et al., 2013; Briel et al., 2010; Spieth et al., 2011b; Talmor et al., 2008; Rouby et al., 2002).

As a result of all these factors, the current standard of MV therapy in the ICU relies heavily on either clinician experience and intuition or a generalised one size fits all approach, such as the ARDSNet PEEP-FiO₂ tables or the protocols used in the ALVEOLI, LOVS, or EXPRESS clinical trials (The ARDS Network, 2000; Brower et al., 2004; Meade et al., 2008; Mercat et al., 2008). However, due to the heterogeneity of patients and the evolution of their lung condition and disease state, a general approach is unlikely to be suitable for all ARDS patients (Sundaresan and Chase, 2011; Hubmayr, 2011a; Gattinoni, 2011a; Gattinoni, 2011b; Hubmayr, 2011b; Ferguson, 2012; Pintado et al., 2013). Therefore, a method to guide patient-specific MV therapy is needed to improve individual patient outcomes.

In this chapter, a comprehensive review of the application of mechanical ventilation in patients with respiratory failure is presented. In particular, an introduction on mechanical ventilation settings and the corresponding adverse effect due to suboptimal MV settings are discussed. This section is followed by the review of several large clinical trials concerning different MV strategies, presented to highlight the need for patient-specific methods to standardise patient-specific MV settings.

2.1 MV Parameters, Measurements and Modes

2.1.1 Breath Parameters – Every Breath Has These

Tidal volume

Physically, tidal volume is the volume of air entering and exiting the patient's lungs for each breath and is usually set by the clinician and reported by the ventilator.

Driving Pressure

Driving pressure or inspiratory pressure is the increase in lung pressure over PEEP during inspiration, and can be clinically limited, if desired.

2.1.2 MV Input Settings

Positive End-Expiratory Pressure (PEEP)

As mentioned, PEEP is the baseline pressure at the end of expiration. Additional pressure and volume are delivered above this baseline. PEEP is used to ensure the lung remains inflated to allow gas-exchange. However, excessive PEEP can cause circulatory depression and increase pulmonary edema (Albert et al., 1985; Pinsky, 1997; Toung et al., 1978). Furthermore, excessive PEEP without accounting for driving pressure, may increase airway pressures and volumes causing overdistension (Brower et al., 2004).

Peak Inspiratory Pressure (PIP)

PIP is the sum of PEEP and driving pressure, and is thus the highest pressure in the lung during inspiration. Often, PIP is set at a limit to avoid ventilation at excessive pressures that may cause further injury (Petersen and Baier, 1983; Parker et al., 1993; Slutsky, 1999). PIP may be limited in pressure control modes where pressure is the independent variable.

Tidal Volume (V_t)

Higher tidal volumes can assist with ventilation of carbon dioxide from the lung in patients with hypercapnia or delivery of oxygen to patients that have hypoxemia. However, excessive volumes can overinflate and stretch the lung tissue causing further injury (Chao and Scheinhorn, 1996; Dreyfuss and Saumon, 1998). The tidal volume is either set or monitored depending on the ventilation mode. Tidal volume may be limited in volume control modes, where it is the independent variable.

Respiratory Rate (RR) and Inspiration to Expiration (I:E) ratio

The RR is the number of breaths that occur per minute and is commonly set around 16-20 so that each breath is approximately 3-4 seconds in length. Spontaneously breathing patients on support modes set this pace themselves, and hybrid modes ensure a maximum period limit.

In controlled modes, within the length of each breath fixed by the RR, clinicians can adjust the I:E ratio - the ratio of inspiration time to expiration time. Typical I:E values are between

1:1.6 and 1:2 allowing significantly more time for passive expiration to ensure adequate ventilation of carbon dioxide out of the lung (Aboab et al., 2012).

Fraction of Inspired Oxygen (FiO_2)

FiO_2 is the oxygen content of the gas delivered to the patient. Air contains approximately 21% oxygen, but higher oxygen content can be delivered by adding pure oxygen. Higher FiO_2 allows patients to better exchange oxygen from their lungs into their blood by increasing the oxygen concentration and thus the rate of diffusion. However, excessive FiO_2 can cause oxygen toxicity and further lung injury (Rachmale et al., 2012). FiO_2 above 21% is often used for patients who, for clinical reasons, cannot be delivered higher pressures or tidal volumes.

2.1.3 MV Modes

Numerous different ventilation modes exist and it is common for each ventilator manufacturer to have their own unique versions of similar ventilation techniques. Fundamentally, there are several different types (Mireles-Cabodevila et al., 2009; Hasan, 2010):

1. Control versus support modes:
 - 1.1. Control modes strictly adhere to the chosen ventilation strategy, commonly used for patients that are heavily sedated, paralyzed or cannot breathe regularly for themselves.
 - 1.2. Support modes are less invasive and assist the patient when spontaneously breathing.
 - 1.3. Hybrid modes, such as synchronized intermittent mandatory ventilation (SIMV), allow patients to control the timing of their breathing while offering support, but also ensure that breaths are given to the patient when no spontaneous effort is made.
2. Pressure versus volume methods:
 - 2.1. Pressure control methods require inputs of PEEP and driving pressure to construct the pressure waveform delivered to the patient. The resulting tidal volume is the dependent outcome.
 - 2.2. Volume control methods require inputs of tidal volume (V_t) and flow profile to construct the volume waveform delivered to the patient. Driving pressure and resulting PIP are thus the dependent outcomes.
 - 2.3. Both pressure or volume control methods can be delivered in either a control mode or support mode.

2.1.4 MV Outcome Measurements

Partial Pressure of Oxygen (PaO₂) or Peripheral Capillary Oxygen Saturation (SpO₂)

Oxygenation of the blood can be measured arterially as PaO₂, or using pulse oximetry reporting SpO₂. Blood oxygenation is the most common monitoring metric to ensure ventilation is adequate and delivering sufficient oxygen to the patient. Standard practice aims for minimum PaO₂ > 80 mmHg (Mellemaard, 1966; Sorbini et al., 1968) and minimum SpO₂ on the order of 88-95% depending on the current FiO₂ (Brower et al., 2004; Meade et al., 2008; Mercat et al., 2008).

Minute Ventilation

Minute ventilation is the volume of air delivered during one minute and is effectively the product of the RR and V_t. Target minute ventilation goals are commonly 8-10 L/min (Soo Hoo, 2005; Robert J. Mason et al., 2010).

Transpulmonary Pressure

PEEP and airway pressure are easily measured parameters, but may not be as clinically applicable as the transpulmonary pressure, the pressure difference between the alveoli and the pleural cavity. Due to the significant heterogeneity of ARDS patients, a set PEEP in different patients may not translate into consistent transpulmonary pressures (Talmor et al., 2006). Since the mechanics of lung collapse, recruitment and overdistension depend on the pressure within the lung, relative to outside the lung in the abdomen and within the pleural cavity, transpulmonary pressures are clearly more relevant than PEEP (Slutsky, 1999). For this reason, MV should provide adequate transpulmonary pressure to maintain acceptable oxygenation, while minimising both atelectasis and overdistension (Slutsky, 1999; Talmor et al., 2008). However, estimating transpulmonary pressure requires the highly invasive use of a balloon catheter to measure the pleural pressure (Talmor et al., 2008) and is thus not clinically applicable at this time.

Invasive / Noninvasive Imaging

Computed Tomography (CT) is a gold standard for monitoring lung condition and recruitment. The CT images allow the clinicians to assess patient condition, response to different PEEP levels, alveoli recruitment / distension, and gas distributions. However, CT for ICU patients is costly and further exposes the patient to risk of radiation exposure

(Brenner and Hall, 2007; Chase et al., 2014; Sundaresan and Chase, 2011). Thus, the application of CT to guide therapy remains limited (Slutsky and Hudson, 2006).

An emerging form of lung imaging is Electrical Impedance Tomography (EIT). EIT is non-invasive and has shown good correlation with CT findings, such that it has been proposed to guide ventilation therapy (Adler et al., 1998; Zhao et al., 2010). However, EIT technology is relatively new and costly (Fagerberg et al., 2009), and there is no definite or standardized guideline for application at this time. More studies are required for this technology to implement it in regular patient care.

2.1.5 Summary:

MV is managed by setting several basic parameters, while checking that other measured parameters are within currently acceptable bounds, while intermittently making small changes to care based on patient response. This section has introduced some of parameters and described their role in current MV practice.

It is common to manually titrate the ventilation parameters to ensure all targets are met, while trying to reduce the risk of further injury. Oxygenation is often monitored, while reducing FiO_2 or PEEP to generally safer levels. However, as noted, there is no consensus on what is “best” or how to reach it.

2.2 The Problems with MV Management

MV is a crucial support therapy for patients with respiratory failure. However, this essential treatment has consequences that can cause further injury or delay recovery. Ventilator induced lung injury (VILI) is caused by non-optimal ventilation and manifests as a mechanical injury to alveoli that exacerbates the systemic inflammation common in ARDS patients (Zilberberg and Epstein, 1998; Dreyfuss and Saumon, 1998; Ranieri et al., 1999; Adams et al., 2003; Ricard et al., 2003; Gajic et al., 2004; Moloney and Griffiths, 2004; Carney et al., 2005; Parsons et al., 2005; Villar, 2005; Pavone et al., 2007). It can directly increase the risk of death (Gajic et al., 2004; Carney et al., 2005), as well as the length and cost of ventilation.

Modern MV is comprised of positive-pressure ventilation that drives air and oxygen into the lung during inspiration and passively lets expiration occur naturally. A healthy lung creates a negative-pressure inside the lung by expanding the chest wall and flexing the diaphragm, and pressure equalisation brings air into the lung. Air is exhaled passively, reducing the volume of the lung. Thus, the non-physiological, added stresses and strains caused by MV may initiate added trauma in any of four categories: barotrauma, volutrauma, atelectrauma, and biotrauma or other.

2.2.1 Effect of Excessive Pressure – Barotrauma

Barotrauma is the injury caused by excessive pressures in the lung. The pressure gradient between the alveoli and the abdomen can cause air to migrate into the interstitial tissue causing many of the manifestations of barotrauma (Slutsky, 1999). Early work by Peterson and Baier (Petersen and Baier, 1983) reported that all patients with PEEP > 40 and/or PIP > 100 cmH₂O developed barotrauma. However, more recently, Weg et al. (Weg et al., 1998) cast doubt on these results when they compared patients with matching disease states (ARDS induced by sepsis) and reported no significant difference in pneumothorax rates for high pressures or volumes. The pressure at incidence is likely patient-specific; to avoid barotrauma in a diverse cohort, pressures significantly lower than PEEP = 40 and PIP = 100 cmH₂O should be employed. Overall, barotrauma is a result of driving pressure or PEEP that is too high, resulting in excessive PIP and lung pressures.

2.2.2 Effect of Excessive Volume – Volutrauma

Excessive volume ventilation, or volutrauma, is observed to stretch the lung tissue beyond its elastic limit. It can lead to pulmonary edema, increased fluid filtration, diffuse damage to alveoli, epithelial and microvascular permeability (Slutsky, 1999). It is a result of too large tidal volume, V_t either by specification or as a result of delivered driving pressure in pressure controlled modes.

2.2.3 Effect of too little volume and/or pressure – Atelectrauma

Atelectrauma is the cyclic opening and closing of alveoli during each breath. Ventilating a patient with respiratory failure provides higher pressures that recruit alveoli during inspiration, but, as the pressure drops, the diseased alveoli collapse. It is a symptom of a PEEP that may be too low to keep such recruited alveoli open. Experimental work has reported that atelectrauma is common in patients diagnosed with ARDS and may be more

significant in ARDS mortality than originally thought (Meade et al., 2008), further indicating a need for optimal patient-specific PEEP.

2.2.4 Biotrauma and other adverse effects related to sub-optimal MV settings

The most difficult lung injury to quantify in a clinical setting is biotrauma: the body's response to the invasion of MV, which can lead to increases in alveolar-capillary permeability, surfactant inactivation and the release of inflammatory mediators (Marini and Gattinoni; Gattinoni et al.; Ferguson et al., 2013). One cause of multiple organ failure and mortality described by Slutsky and Tremblay (Slutsky and Tremblay, 1998) and later confirmed in an animal study by Murphy et al. (Murphy et al., 2000) is that non-protective ventilation strategies ($V_t \sim 12$ mL/kg and PEEP = 0 cmH₂O) are associated with bacterial translocation and the transmission of pulmonary infections and inflammatory mediators into the circulatory system with subsequent systemic inflammation compared to protective ventilation strategies with moderate PEEP (10 – 12.5 cmH₂O) and lower tidal volume ventilation (~ 5 mL/kg).

Other adverse effects of MV include ventilator associated pneumonia (Cook et al.), pulmonary edema or fluid build-up in the lung (Brower et al., 2004), circulatory depression or a reduction in cardiac output due to increased chest cavity pressures (Brower et al., 2004), oxygen toxicity due to excessive oxygen (Ferguson et al., 2013; Slutsky, 1999), and hypercapnia or excessive CO₂ caused by too little ventilation of CO₂ out of the blood. All of these effects increase the risk of poor outcome. Equally, the latter two are also a result of sub-optimal ventilation parameters and management.

2.2.5 ARDS Diagnosis as a ratio of blood oxygenation to inspired oxygen and other factors

Various pulmonary and extrapulmonary insults may lead to a patient developing respiratory failure. The most frequent are pneumonia and extrapulmonary sepsis (Sigurdsson et al., 2013; Rubenfeld and Herridge, 2007; Fan et al., 2008). A severe form of respiratory failure is ARDS. In 1994, the American-European Consensus Conference (AECC) defined diagnostic criteria for ALI and ARDS (Bernard et al., 1994):

Table 2.1. AECC Definition of ARDS.

Timing:	Acute and sudden onset of severe respiratory distress;
Chest imaging:	Bilateral infiltrates on frontal chest radiograph;
Hemodynamics:	The absence of left atrial hypertension (a pulmonary capillary wedge pressure <18 mmHg or no clinical signs of left ventricular failure); and
Oxygenation:	Severe hypoxemia (assessed by the $\text{PaO}_2/\text{FiO}_2$ ratio), where:
	<ul style="list-style-type: none"> a. ALI exists when the $\text{PaO}_2/\text{FiO}_2$ ratio is ≤ 300 and >200 mmHg regardless of the PEEP and FiO_2, and b. ARDS exists when the $\text{PaO}_2/\text{FiO}_2$ ratio is ≤ 200 mmHg again regardless of PEEP and FiO_2.

The AECC definition has been adapted in an attempt to better capture the syndrome. This new definition is referred to as the Berlin definition (The ARDS Definition Task Force, 2012):

Table 2.2. Berlin Definition of ARDS.

Timing:	Onset of ARDS within 1 week of a known clinical insult or new or worsening respiratory symptoms.
Chest imaging:	Either chest radiograph or CT scan reporting bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules.
Origin of edema:	Respiratory failure not fully explained by cardiac failure or fluid overload. Requires objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present.
Oxygenation:	$\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg with PEEP ≥ 5 cmH ₂ O for mild ARDS, < 200 or < 100 mm Hg for moderate or severe ARDS.

The requirement of chest imaging before diagnosis and treatment of ARDS is a major disadvantage of the ARDS definition and standard practice. To provide prompt recruitment and maintenance, a RM should be performed as soon as possible for any MV patient to open up the lung and assist with gas exchange (Borges et al., 2006; de Matos et al., 2012). Diagnosis could then follow patient stabilization.

ARDS is typically diagnosed at one moment in time near the start of ventilation (Estenssoro et al., 2003). However, the current PEEP at that time can greatly effect both the measured PaO_2 and the required FiO_2 for adequate oxygenation. Estenssoro et al. (Estenssoro et al.,

2003) reported that PEEP greater than zero during initial ventilation can improve PaO_2 so drastically that ARDS may be misdiagnosed if assessment is delayed too long, due to delay in blood gas extraction or waiting for chest imaging results. If each patient had been evaluated 6 hours later, 52% would no longer fulfil the AECC definition for ARDS ($\text{P/F} < 200$) and instead be diagnosed with less severe ARDS or ALI (Estenssoro et al., 2003), possibly changing their overall treatment and care. In this study, no RMs were performed, and Estenssoro et al. attributed the improvement in P/F ratio from < 200 to > 200 over 24 hours for 18 of the 48 similarly ventilated patients to a relatively higher mean PEEP of 12.8 cmH_2O after 24 hours.

Villar et al. (2007) conducted a similar trial to Estenssoro et al., where patients were tracked. Approximately 40% of ARDS patients exhibited an increase in P/F ratio to above the AECC threshold when evaluated after 24 hours at $\text{PEEP} \geq 10 \text{ cmH}_2\text{O}$ and $\text{FiO}_2 \geq 50\%$. Villar and Kacmarek (2012) warns that all respiratory failure patients start off with poor oxygenation and neither the AECC or Berlin definitions allows for re-evaluation of hypoxemia at consistent ventilator settings, in particular PEEP and FiO_2 . They continued to recommend the use of a PEEP and FiO_2 trial conducted 24 hours after ARDS diagnosis stating this would be an easy and simple strategy to identify subpopulations and provide care based on the patient's risk (Villar and Kacmarek, 2012).

Defining ARDS/ALI within respiratory failure is an important step towards distinguishing between severe and moderate respiratory failure and providing appropriate care. However, diagnosis of ARDS is slow and followed by rapid patient evolution. Care must be taken not to misdiagnose patients at the wrong time. What is needed is a consistent standard of care to provide early ventilation support for any and all patients requiring respiratory support so that patients can be diagnosed when convenient. These results also clearly show the need for patient-specific MV that can evolve as dynamically as the patient in the first 24-48 hours.

2.2.6 The problem with patients – heterogeneity in affected lung and response

The lung of a patient with ALI or ARDS is very heterogeneous, with mixed healthy and diseased alveoli, thus displaying significant inter- and intra- patient variability. Thus, what works for one patient may lead to VILI in another (Chiew et al., 2011; Thammanomai et al., 2013). Equally, what helps a diseased alveoli may injure a nearby healthy alveoli.

Inter-patient variability in heterogeneity of disease and response

Within a cohort of ARDS or respiratory failure patients, the primary diagnosis is often not recorded as ARDS (Ware and Matthay, 2000; Matthay et al., 2012) and the etiology of respiratory failure varies with each patient (Artigas et al., 1998; The ARDS Definition Task Force, 2012). Although the most frequent causes are pneumonia and extrapulmonary sepsis, very diverse cohorts have been included in ARDS or respiratory failure studies (Artigas et al., 1998; The ARDS Definition Task Force, 2012). With the diverse causes of respiratory failure comes a wide distribution of lung condition and thus individual patient-specific requirements in optimal ventilation settings.

Intra-patient variability 1: in evolution of disease over time (need for real-time vs intermittent)

Each patient will respond to treatment and ventilation support differently. The progression of disease over time will affect their lung condition and the parameters for their optimal ventilation. Hence, care must be able to measure appropriate metrics of patient-specific lung condition to evolve over time.

Intra-patient variability 2: heterogeneity of the lung in ARDS or response to MV in respiratory failure

Within the ARDS or respiratory failure lung, it is common for some areas to be collapsed (atelectasis) and poorly perfused, while others are normal. MV cannot provide ventilation separately to the heterogeneous lung areas. Considering both lungs, each with significant variability, selection of 'optimal' ventilation settings for overall lung recruitment can provide excessive pressures/volumes to some regions, while providing too little to others. Lung injury can thus be exacerbated by attempting to provide improved care by further injuring non-aerated, collapsed alveoli.

2.2.7 Summary:

MV management is a therapy that must carefully balance different settings. Insufficient or excessive support will result in potential harm to the patients, prolonging their dependency of MV. This issue is exacerbated by inter-patient variability in response across cohorts, as well as by intra-patient variability in the evolution of condition. There is thus a strong need for optimal titration mechanisms that are patient-specific, specific to disease state, and can evolve dynamically, in real-time to patient condition.

2.3 MV Strategies and Trials: To overcome these issues

2.3.1 Lung recruitment strategies: Recruitment Manoeuvres

Recruitment defined by Fan et al. (Fan et al., 2008) is the “dynamic process of reopening unstable airless alveoli through an intentional transient increase in transpulmonary pressure”. RMs have shown to promote alveolar recruitment, increase end-expiratory volume, improve gas exchange, and attenuate VILI by preventing atelectrauma. (Fan et al., 2008). The tidal cycle during a RM shifts to where cyclic derecruitment is less likely to occur during the respiratory cycle given that PEEP > closing pressure of the majority of alveoli. However, Rose (Rose, 2010) described how effective RMs are difficult to conduct due to the heterogeneity of patients, and their response to pressure. Specifically, some may overdistend and others may fail to recruit (Suarez-Sipmann et al., 2007), as elastance, the patient-specific response to pressure and volume varies.

Thus, different types of RMs have been studied with inspiratory pressures anywhere between 30 and 60 cmH₂O (Borges et al., 2006). Sustained inflations or breath holding sessions for up to 40 seconds, intermittent sighs with high pressure or volume, and incremental increases in PEEP and/or PI are common types of RM. However, trials testing RMs have failed to produce consistent results and the best method is yet to be confirmed (The ARDS Network, 2003; Fan et al., 2008). Evidence does suggest that high pressure RMs may overinflate parts of the heterogeneous ARDS or respiratory failure lung (Carvalho et al., 2007), and temporarily cause circulatory depression (Odenstedt et al., 2005).

More specifically, factors such as the method (e.g. breath holding vs. staircase PEEP), timing (e.g. early vs. late) and underlying etiology of ALI/ARDS (e.g. pulmonary vs. extrapulmonary) are reported to be important factors in the efficacy of RMs (Fan et al., 2008). Early in the disease, atelectasis is reversible and the lung may be easily recruitable without negative side effects (Grasso et al., 2002). Equally, some researchers have reported that not all patients benefit from an RM (Guerin, 2011) or have recruitable lung volume (Estenssoro et al., 2003). Thus, there remains a lack of confirmation of the long term management, adverse effects, and generality of these findings in non-selected populations.

By transiently increasing pressure in the lung, collapsed or non-aerated alveoli have time to open and recruit. Alveolar recruitment increases the aerated lung volume aiding gas exchange and perfusion. The clinical benefits of RMs, particularly early in care, are numerous.

However, the efficacy of RMs degrade over time as the lung settles into a collapsed state and is thus again, more difficult to recruit (Rocco et al., 2010; Gattinoni et al., 2006). The links between respiratory failure severity, recruitability and other outcome measurements require further investigation in large randomized trials.

2.3.2 Compliance strategies

Static compliance ($1/\text{elastance}$) has been reported to change significantly with both tidal volume and PEEP (Suter et al., 1975; Suter et al., 1978) (Venegas et al., 1998; Harris et al., 2000). The local maxima of compliance at a patient-specific PEEP was noted to be dependent on the ventilated tidal volume and explained in terms of position on the static PV curve (Suter et al., 1975; Suter et al., 1978) (Venegas et al., 1998; Harris et al., 2000). In general, higher tidal volumes reduce the PEEP of maximum compliance (Suter et al., 1975; Suter et al., 1978) (Venegas et al., 1998; Harris et al., 2000).

The gold-standard approach to obtain a static PV curve is the super syringe method that fills the lung before emptying it in a controlled stepwise manner allowing equilibrium in between each step. The points are connected to form the sigmoidal static PV curve. The produced loop can be used to optimise PEEP and tidal volume. Specifically, PEEP can be set in between the lower inflection point (LIP) and upper inflection point (UIP) of the static PV curve. The super syringe method is clinically cumbersome and highly invasive, as it requires detachment from the ventilator (Lu and Rouby, 2000; Harris, 2005) for up to fifteen minutes (Sundaresan and Chase, 2011). Static PV curves can be obtained directly from some modern ventilators, but require the patients to be sedated and thus are still invasive and a significant interruption to care (Sundaresan and Chase, 2011).

Stahl et al. (Stahl et al., 2006) described the potential in monitoring dynamic respiratory mechanics over incremental PEEP, such as a staircase RM, to estimate both mechanics and recruitment simultaneously. They reported that dynamic respiratory mechanics could be used as a diagnostic tool and would be more appropriate than using static mechanics (Stahl et al., 2006). Comparing static and dynamic compliance Stahl reported that dynamic compliance was less than static compliance, but the difference was dependent on alveolar pressure.

Overall, static compliance neglects airway resistance and misrepresents the dynamics of the lung by assuming a static or quasi-static condition. Monitoring dynamic compliance reports smaller compliance (higher elastance) values, indicating the significance of dynamic effects.

Tracking dynamic compliance is possible breath-to-breath over incremental PEEP. Thus, using dynamic compliance or elastance as a surrogate of lung condition can be used to quantify recruitment and guide care.

2.3.3 Lung protective strategies

As a result of the difficulties and risks of MV, the goals of MV have changed over the last two decades to focus on minimising VILI while maintaining acceptable ventilation. (Ferguson et al., 2013). Avoiding atelectasis and overdistension of alveoli can attenuate alveolar and systematic inflammatory responses (Rouby et al., 2002) and should translate into a measureable improvement in ARDS/ALI patient outcomes (Slutsky, 1999). Hence, protection or risk mitigation has become a primary treatment endpoint.

A protective ventilation strategy is one aiming to minimise VILI and find a balance between oxygenation and CO₂ elimination targets. Rose (Rose, 2010) described the “*mortality reducing effect of lung protective ventilation using low tidal volumes and pressure limitation*” to prevent alveolar collapse or overdistention in ARDS patients. It is also suggested that these strategies may also be beneficial in patients with normal lungs. The following summarises several lung protective strategies that were carried out over the years.

ARDSNet:

The ARDS Net strategy aims to minimise stretch-induced lung injury, while maintaining acceptable oxygenation, by ventilating with small tidal volumes (≤ 6 mL/kg) and plateau pressures lower than 30 cmH₂O (Spieth et al., 2011b). The ARDSNet trial showed that lower tidal volumes (6.2 ± 0.8 mL/kg) are better than higher (11.8 ± 0.8 mL/kg). This low V_t strategy uses tables of fixed combinations of FiO₂ and PEEP that are periodically adjusted to maintain oxygenation goals (Spieth et al., 2011b). ARDS Net is easy to follow, but relies on the relationship between PaO₂ and FiO₂ being generic to all patients at all times as their condition evolves.

However, the physiological rationale and the lack of individuality has been questioned (Spieth et al., 2011b). The ARDS Net protocol may also be associated with increased atelectasis owing to the low PEEP used and the lack of RMs (Spieth et al., 2011b). Thus, to avoid VILI by minimising lung strain and further improving care, the ideal tidal volume should be monitored in a patient-specific breath-by-breath or high time resolution approach similar to PEEP (Sundaresan and Chase, 2011).

OLA:

The open lung approach (OLA) aims to open and maintain lung recruitment. It also reduces dynamic strain (Spieth et al., 2011b). RMs are used to open up the lung and PEEP is titrated to gas exchange or respiratory variables to maintain recruitment, avoiding cyclic collapse/re-opening (Spieth et al., 2011b). One OLA strategy of setting PEEP just above the inflection point of a static pressure-volume curve has shown promise by reducing inflammatory mediators in bronchoalveolar lavage fluid and blood samples

The three most significant clinical tests of the OLA are ALVEOLI (Brower et al., 2004), LOVS (Meade et al., 2008), and EXPRESS (Mercat et al., 2008). ALVEOLI used two predetermined PEEP-FiO₂ tables to ensure SpO₂ was within acceptable limits of 88 to 95% (Brower et al., 2004). The lower PEEP group represented clinical consensus in 1995 whereas the higher PEEP group reflected the beneficial results of Amato et al (Amato et al., 1998). ALVEOLI used a target V_t of 6 mL/kg predicted body weight with PIP limited to 30 cmH₂O or less. LOVS also utilised PEEP-FiO₂ tables with V_t of 6 mL/kg, but conducted a 40 second breath-hold at 40 cmH₂O with FiO₂ of 1.0 and thus allowed PIP up to 40 cmH₂O. EXPRESS took a different approach by adjusting FiO₂ to maintain oxygenation goals and for the control minimal distension group. PEEP and PIP were kept as low as possible without dropping out of acceptable oxygenation. Within the increased recruitment group, PEEP was kept as high as possible preventing PIP rising above 30 cmH₂O regardless of the effect on oxygenation. None of these three large multi-centre trials conclusively reported any benefit of the OLA or higher PEEP ventilation. However, EXPRESS did report a significant improvement in ventilator free-days (median [IQR]: 7 [0-19] vs. 3 [0-17], p=0.04). Although the primary outcome of mortality failed to reach significance, benefits including higher compliance values, improved oxygenation (Brower et al., 2004; Mercat et al., 2008), and reduced rates of, and death from, refractory hypoxemia (Meade et al., 2008).

An early small trial by Amato et al. (Amato et al., 1998) reported a benefit from ventilation above the LIP on a PV curve compared to standard ventilation. Mortality was reduced from 71% to 38% and rates of barotrauma were greatly reduced (n=53, p<0.001). Villar et al. (Villar et al., 2006) conducted a similar trial later setting PEEP 2 cmH₂O higher than the LIP and reported significant improvements in ICU and hospital mortality, ventilator free days, and organ failures (n=95). However, Oba et al. (Oba et al., 2009) argued that the static pressure-volume curve may not be the best way to select optimal PEEP for an OLA.

Spieth et al. (Spieth et al., 2011b) conducted a recent animal trial involving pigs with surfactant washout induced ARDS randomised into either the standard ARDS Net protocol (PEEP = 12 cmH₂O) or an open lung approach (OLA) with PEEP set to minimal respiratory elastance. PEEP and mean airway pressure were higher in OLA. OLA was associated with improved oxygenation after 6 hours and redistributed pulmonary perfusion, but with more alveolar overdistension, while ARDS Net was associated with more intra-alveolar haemorrhage. Inflammatory mediators and markers of lung parenchymal stress did not differ significantly. Better redistribution of pulmonary blood flow in the OLA approach may contribute to better ventilation-perfusion matching and the reported improved oxygenation. Therefore, a patient-specific OLA strategy providing PEEP corresponding to minimal elastance is beneficial in pigs but should be tested in a randomized controlled trial.

Overall, minor clinical benefits of OLA strategies have been shown in different studies. However, the improvement in primary patient outcomes have not yet been fully established by large multi-centre trials (Amato et al., 1998; Villar et al., 2006; Brower et al., 2004; Meade et al., 2008; Mercat et al., 2008). The more recent OLA results by Spieth et al point towards a patient-specific elastance as a means of obtaining the best benefits of an OLA approach.

2.3.4 Variable ventilation strategies

Healthy physiological systems exhibit a natural variability that leads to greater flexibility and more robust function compared to diseased systems. In contrast, a low variability breathing pattern may be observed in MV patients who failed to wean from MV. Thus, it has been proposed to reintroduce variability to replicate this behaviour (Suki et al., 1998).

Variable controlled ventilation has been associated with improved oxygenation, a reduction in mean peak airway pressure, as well as improved pulmonary function in several animal studies (Funk et al., 2004; Mutch et al., 2000; Gama de Abreu et al.; Spieth et al., 2009b; Spieth et al., 2011a). The best results occur when tidal volume variability matches the variability in healthy subjects (Spieth et al., 2009a). The mechanisms responsible may include recruitment, surfactant release and improved volume/flow matching as a consequence of the redistribution of pulmonary blood flow (Gama de Abreu et al., 2008; Spieth et al., 2009b).

Variable tidal volumes improve pulmonary function by replicating natural variability. However, the benefits have yet to be conclusively reported in human trials and the causation of improved oxygenation resulting in better patient outcomes are yet to be shown. The benefits are likely to be more substantial for patients ventilated for long durations.

2.3.5 High Frequency Oscillation (HFO) and Airway Pressure Release Ventilation (APRV) strategies

In both these approaches, a relatively high mean airway pressure, referred to as ‘continuous distending pressure’ in HFO or ‘P_{high}’ in APRV, is used to maintain a healthy end-expiratory lung volume and adequate oxygenation levels. Both methods promote alveolar recruitment and maintenance due to the continuously elevated pressure within the lung, minimising atelectasis as the minimum pressure is relatively high. Recruitment not only depends on the pressure in the lung, but also the duration that pressure is held, where elevated pressures for a relatively long time can assist with opening more stubborn alveoli.

HFO ventilation uses rapid application of small tidal volume breaths with a large mean airway pressure to ensure adequate oxygenation (Ferguson et al., 2013). The majority of HFO studies treated neonatal patients and reported small reductions in chronic lung disease (Ferguson et al., 2013). Recent studies to compare HFO with conventional MV have reported promising physiological and inflammatory results (Ferguson et al., 2013). One downside of HFO is that the patient usually requires sedation whereas during APRV, the patient does not necessarily need to be sedated and ideally should be spontaneously breathing to assist CO₂ respiration.

APRV is similar to HFO, but includes brief periods where the pressure is dropped to release air from the lungs and eliminate CO₂. These pressure releases must be kept brief to prevent the pressure dropping to a point where the alveoli may start to collapse. The pressure releases are crucial to eliminate respired CO₂ out of the lung. Thus, patients that have hypercapnia should be ventilated with more frequent or longer duration releases, whereas patients that have hypoxemia require fewer and shorter releases requiring patient-specific adjustment (Rasanen et al., 1991). APRV facilitates spontaneous breathing and has been associated with progressive recruitment (Sydow et al., 1994), improved oxygenation (Habashi, 2005), reduced peak airway pressures (Sydow et al., 1994; Habashi, 2005), and improved volume/flow matching (Putensen et al., 1999).

Although HFO and APRV are protective strategies operating on similar principles their applications are quite different. HFO requires sedation and has not been conclusively proven in adult human trials. APRV on the other hand, has been shown to be clinically beneficial in spontaneously breathing patients.

2.3.6 Transpulmonary Pressure and oesophageal pressure PEEP titration

Talmor et al. (Talmor et al., 2008:) used an esophageal balloon catheter estimating pleural pressure to adjust PEEP with a predetermined $\text{FiO}_2\text{-P}_{\text{Lexp}}$ table, to maintain positive but small transpulmonary pressures, and compared against a control group ventilated based on the ARDS Net standard of care (The ARDS Network, 2000). The P/F ratio was higher in the intervention group at 72 hours ($p=0.002$) and compliance was significantly better ($P=0.01$). This result demonstrates the value of pleural pressure, but its invasiveness is not abated.

2.3.7 Summary

In summary, it is clear that no general, one size fits all protocol is fully successful. Hence, it is equally clear that respiratory failure patients requiring mechanical ventilation are highly variable and there is a need to manage mechanical ventilation strategy based on patient-specific needs. It is thus very important to have the means to assess the dynamic changes in patient-specific respiratory disease state regularly in clinical real-time without additional invasive measurements or interruptions to care.

Recently, model-based therapy has emerged as a potential solution to manage specificity in patient disease and response to treatment (Schranz et al., 2013; Rees, 2011; Ionescu et al., 2014). In particular, mathematical models describing the breath-by-breath patient-specific respiratory system mechanics can provide unique information to patients' condition in real time, in particular, elastance. These information were translated to medical decision support metric to guide bedside mechanical ventilation therapy (Rees, 2011; Thomsen et al., 2013). Coupled with regular recruitment and other protective lung strategies, model-based treatment offers the opportunity for clinicians to provide patient-specific therapy in a consistent fashion.

2.4 The real needs highlighted

2.4.1 Managing intra-patient variability → real-time, breath-to-breath

The lung of an ARDS or respiratory failure patient can change dramatically over the first 24 hours of ventilation. The lung condition improves with suitable MV, which can significantly alter the patient's need for subsequent ventilation. Thus, instead of selecting PEEP once, such as Amato et al. (Amato et al., 1998) and Villar et al. (Villar et al., 2006) using PV curves at the start of MV, ventilation settings should be constantly titrated, either breath-to-breath or very regularly, in real-time or to evolve with the patient and reflect their current condition.

2.4.2 Managing inter- and intra- patient variability using a measurable metric for patient-specific titration → minimising respiratory elastance

Due to the inter- and intra- patient heterogeneity discussed in Section 2.2.6, ventilating cohorts of respiratory failure patients with generalised approaches will not cater for individual patient-specific ventilation needs. What is needed is the ability to accurately or effectively assess lung condition non-invasively, in real-time with no interruption to ventilation.

By using a simple model, lung elastance can be calculated with the airway pressure and flow data. Tracking elastance over time provides a clinically useful surrogate to patient condition, and patient-specific response to pressure and volume, that can be used with incremental PEEP changes to determine an optimal PEEP for continued support.

2.4.3 Recruit the lung and assess patient-specific response to pressure → use of regular RM

Over time, patient-specific lung condition changes and previously recruited alveoli may start to collapse. A RM will attempt to recruit any alveoli that were collapsed. The changing PEEP of a staircase RM allows inspection of lung condition, via elastance, over a wide range of PEEP that can then be used to select the optimal PEEP given the current ventilation settings and patient state. Regular smaller incremental PEEP RMs will assist maintenance of an open-lung by reopening any recently collapsed alveoli and provides a convenient mode of PEEP titration for daily or more frequent adjustments to PEEP to reflect changing lung condition.

2.5 The need of Model-Based mechanical ventilation

2.5.1 Models and background

Recently, several new model-based metrics for assessing patient-specific lung elastance (Chiew et al., 2011; Chiew et al., 2012; Chiew et al., 2015c; Rees, 2011; Pomprapa et al., 2014), recruitment (Sundaresan et al., 2009; Sundaresan and Chase, 2011) (Rees, 2011; Pomprapa et al., 2014), and recruitment or lung volume response to MV (Sundaresan et al., 2011b) (Rees, 2011; Pomprapa et al., 2014) have been developed. Importantly, they all offer insight into patient-specific condition that is not available via typical static surrogate estimates (Lucangelo et al., 2007; Brochard et al., 2012), and, equally, they can be estimated breath-to-breath, and monitored as a surrogate of patient condition, as well as potentially being used to guide therapy (Chiew et al., 2011; Sundaresan et al., 2011a; Rees, 2011; Pomprapa et al., 2014). In particular, the single-compartment model (Bates, 2009), arguably the simplest respiratory system model (Lucangelo et al., 2007; Ben-Tal, 2012), is physiologically relevant, has been clinically validated (Sundaresan et al., 2009; Sundaresan et al., 2011a) and offers the potential to guide MV therapy decisions. However, to date, it has not yet been used to prospectively guide therapy directly (Chiew et al., 2011; Sundaresan et al., 2011a), although pilot trials have been run (Davidson et al., 2014; Chiew et al., 2015c).

Experimental animal trials by Carvalho et al. (2007), Suarez-Sipmann et al. (2007), and Lambermont et al. (2008) have reported that ARDS induced pigs experienced a minimal respiratory elastance at a specific PEEP associated with higher oxygenation, maximum recruitment, and higher functional residual capacity all without signs of lung overdistension. Carvalho et al. tracked the breath-to-breath respiratory elastance, of ALI induced piglets during a decremental PEEP trial, and reported that elastance correlated well with the quantity of normally aerated lung volume measured by CT (Carvalho et al., 2007). Thus, supporting the hypothesis by Suter et al. (Suter et al., 1975) that PEEP at maximum compliance or minimum elastance provides the best compromise between recruitment and overdistension.

It has been proposed that setting PEEP to where the lung has minimal respiratory elastance, or maximum compliance, where $\text{elastance} = 1/\text{compliance}$, would be clinically beneficial by balancing the risks of PEEP too low or too high (Suter et al., 1975; Carvalho et al., 2007; Lambermont et al., 2008; Chiew et al., 2011; Pintado et al., 2013). Pilot trials have shown the potential benefit of minimal-elastance PEEP selection (Chiew et al., 2011; Davidson et al.,

2014; Chiew et al., 2015c). Despite the significance of these findings, the application of minimal elastance PEEP selection is obstructed by the complete lack of an easy to use method available at the bedside (Chiew et al., 2015c).

2.5.2 Minimum vs inflection elastance

It has been argued that PEEP should be selected just lower or higher than minimal elastance, referred to as inflection-elastance, as a precaution to prevent negative clinical effects caused by overdistension, while retaining the benefits of recruitment and titrating PEEP (Chiew et al., 2011; Chiew et al., 2015c). Using a valid model, the minimum or inflection-elastance can be found for any mechanically ventilated patient and thus could provide a means to individualise PEEP settings (Chiew et al., 2015c). However, the clinical benefit of ventilating a patient at PEEP selected with either inflection- or minimum-elastance remains to be investigated (Chiew et al., 2015c)

Similar to the PEEP values lying between the two inflection points on a static pressure-volume curve, there is also debate about the optimal choice of PEEP using elastance. Alveolar recruitment is not replaced by overdistension suddenly. Due to the heterogeneity of the ARDS patient lung it also occurs incrementally with pressure. The difference between minimum and inflection-elastance is thus likely to be small and significantly less than the difference from standard practice PEEP.

2.5.3 PEEP selection via regular RM

Recruitment manoeuvres were found to be beneficial to improve recruitment and reduce pulmonary shunting. In addition, it is common that the patient will undergo a RM prior to PEEP titration (Suarez-Sipmann and Bohm, 2009). Hence, clinical protocols that were designed to titrate patient-specific PEEP requires a RM before the actual PEEP titration can begin.

2.6 Chapter Summary:

In summary, existing MV management is generalised and not patient-specific and thus unable to manage patient variability. Hence, there is a need for a strategy that can individualise MV. Model-based ventilation has been gaining ground in MV management, specifically, PEEP selection through observing minimal elastance PEEP during a recruitment and PEEP titration manoeuvre. In the subsequent chapters, a clinical trial designed based on the model-based concept is presented. This trial is named Clinical Utilisation of Respiratory Elastance (CURE) trial. It is a single centre randomised controlled trial designed as an attempt to provide patient-specific MV management and to investigate the effect of its treatment compared to standard practice MV management.

3.0 Model-Based Mechanical Ventilation: Application in a Clinical Setting in Real-Time

3.1 Model-Based Ventilation Theory

Starting with Suter et al. (Suter et al., 1975; Suter et al., 1978) observing that maximum respiratory compliance can be used to estimate optimum cardiopulmonary function and compliance peaks at some PEEP setting for a given tidal volume, researchers have proposed that ventilating at this maximum compliance or minimum elastance would be clinically beneficial. The maximum compliance PEEP represents the critical point, both mathematically and clinically, where to either side the ventilation is inferior. As discussed in depth in Chapter 2.0, at low PEEP the ARDS lung is stiff, under-inflated and is not being used at its capacity. Conversely, at high PEEP the ARDS lung is stiff, over-inflated and the tissue is being physically overstretched.

The clinical application of ventilation at maximum compliance, or minimum elastance, is wrought with difficulties. Not only does the critical point shift with changes in tidal volume, but since the individual patient's condition defines the compliance/elastance as the patient's condition changes, simply by rolling over, the lung compliance/elastance shifts. It is currently impossible to monitor respiratory elastance without invasive measurements or a model-based approach.

As discussed in Chapter 2.0, compliance can be estimated using end-inspiratory pauses or more invasive procedures, such as the super syringe method. Regardless of the model used, titration over PEEP settings for a given tidal volume is required to inspect the compliance/elastance curve and locate the critical point to influence subsequent ventilation. Hence, regular monitoring is required.

3.1.1 Pilot Trials

A proof of concept animal study by van Drunen et al. (van Drunen et al., 2013) described the potential of continuous monitoring of respiratory mechanics in clinical practice. It compared several methods of estimating respiratory mechanics. It concluded that the ability to identify

and track clinically relevant responses to disease progression and MV in real-time shows significant new clinical potential.

Pintado et al. (Pintado et al., 2013) conducted a pilot study comparing individualised PEEP set at highest respiratory system compliance (lowest elastance) against standard practice ARDS Network FiO₂ guided ventilation. Multiple-organ-dysfunction-free days (median 6.0 vs 20.5 days), respiratory-failure-free days (median 7.5 vs 14.5 days), and hemodynamic-failure-free days (median 16 vs 22 days) at 28 days were significantly lower in subjects with compliance-guided PEEP. However, the pilot study failed to meet significance comparing PaO₂/FIO₂ during the first 14 days and in 28-day mortality (20.6% vs. 38.9%).

In particular, in Pintado et al. (2013), PEEP was set daily for the compliance-guided group according to the method described by Suter et al. (Suter et al., 1978). Static compliance was calculated as tidal volume divided by the pressure difference over a 2 s end-inspiratory pause. The PEEP with the highest static compliance was, minimum static elastance, considered best and selected for subsequent ventilation.

3.1.2 Single-Compartment Model and Physiology

Without any additional intrusion to the patient or interruption to their tidal ventilation, a simple model that uses the easily available output pressure and flow data could estimate respiratory elastance for every breath (Chiew et al., 2011). This information can track the patient's condition over changing ventilation settings and help quantify recruitment and locate the maximum compliance (minimal elastance) PEEP. As mechanics change with condition, it can also track condition by this surrogate.

The Single-Compartment Model

The single-compartment model is arguably the simplest respiratory model represented by Figure 3.1 and defined mathematically by Equation 1 (Bates, 2009; Chiew et al., 2011):

$$P_{aw}(t) = R_{rs} \cdot Q(t) + E_{rs} \cdot V(t) + P_0 \quad (1)$$

Where,

P_{aw} - Airway pressure

t - Time

R_{rs} - Airway resistance

Q - Air flow

E_{rs} - Respiratory System Elastance

V - Lung volume

P_0 - Offset pressure (PEEP).

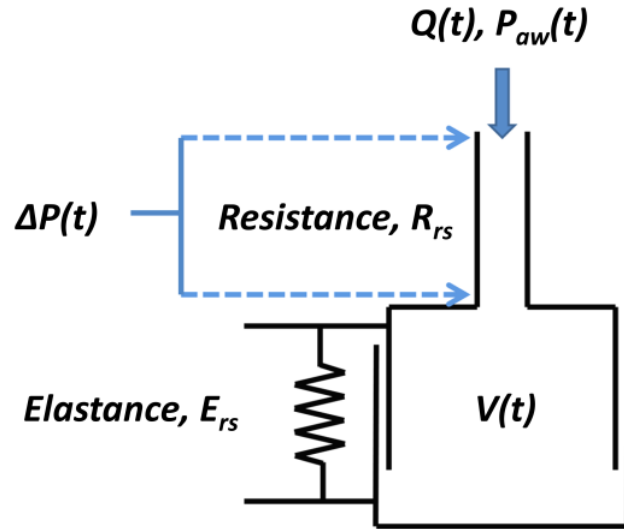


Figure 3.1. Schematic diagram of single-compartment model.

The single-compartment model is applied over inspiration as described in Figure 3.2. The red line is the original data and blue line is the model fitted pressure. The data is fit using an integral based identification method (Hann et al., 2005).

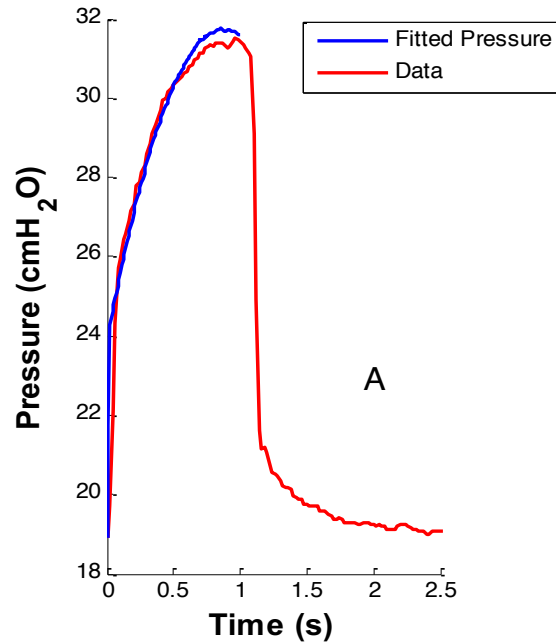


Figure 3.2. Single-compartment model fitting over an inspiration breathing waveform.

One of the major benefits of a simple model is the ease of relating the model parameters to physiology (Docherty et al., 2011). In the case of the single-compartment model, the airway resistance, R , represents the fluid minor losses of the air flowing through the airways (tracheal, bronchus and bronchial) and the respiratory elastance, E_{rs} , represents the stiffness of the lung tissue and other elastic components (chestwall and alveoli). This information can be used as a surrogate of lung condition, as the overall method is identifiable.

Preliminary research by Chiew et al. (Chiew et al., 2011; Chiew et al., 2012; Chiew et al., 2015c) has described how tracking respiratory elastance over time can reflect changes in patient lung condition. In particular, tracking respiratory elastance over incrementally changing PEEP settings, such as a staircase recruitment manoeuvre (RM), can illustrate how respiratory elastance can change with PEEP, as shown in Figure 3.3. The reduction in elastance between the increasing PEEP and decreasing PEEP paths can be explained as an improvement in the patient's condition or lung recruitment.

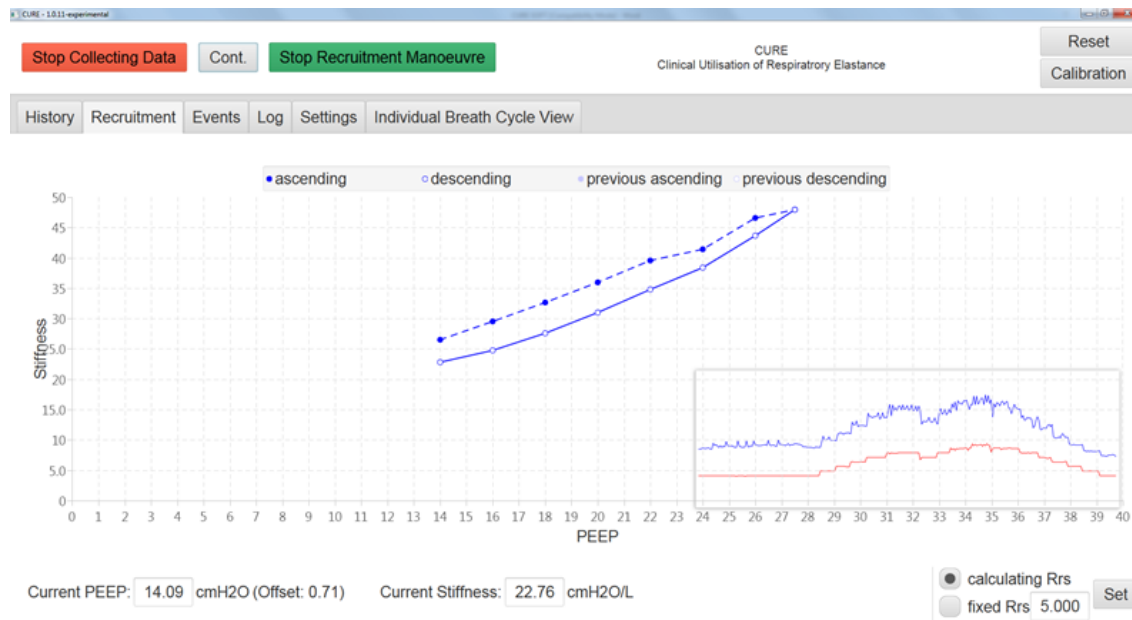


Figure 3.3. Elastance (stiffness) against PEEP plot illustrating recruitment in a continuous monitoring software (Szlavecz et al., 2014).

Szlavecz et al. (Szlavecz et al., 2014) contributed to the feasibility of model-based MV by creating a software platform (CURE Soft). This software monitors mechanical ventilation in real-time by tracking breath-to-breath respiratory elastance. It also provides a tool in plotting elastance against PEEP to visualise recruitment and calculate and suggest the minimal elastance PEEP setting for subsequent care.

Known causes of respiratory system elastance change, such as administration of muscle relaxants and changes in PEEP were used to validate the software. The researchers demonstrated that the system is able to provide detailed, previously unavailable information on patient-specific respiratory mechanics and response to therapy in real-time. This added insight available to clinicians provides the potential for more informed decision-making, and thus improved patient care and outcomes.

Clinical Utilisation of Respiratory Elastance Software (CURE Soft) was developed with the plan of implementing in a clinical randomised controlled trial (RCT) to test the efficacy of model-based MV. CURE Soft is compatible with any device running Java and can easily be customised for the purpose be it research or clinical use. Section 5.4 presents more detailed information regarding CURE Soft amendments for implementation by clinicians in CURE RCT.

3.2 The Early Plan and Primary Goal for Hardware

During the two previous CURE pilot trials (Szlavec et al., 2014; Chiew et al., 2015c), laptop computers were used to acquire data at the bedside for monitoring. Laptops require an additional medical trolley, and cables connecting to a power supply and the ventilator inside a confined bed-space. Each ICU bed-space already contains a bed, at least two trolleys, a ventilator, two ceiling mounted monitors, and all the associated cables and tubing, and any other medical device the patient requires. However, the primary goal of the CURE Soft hardware installation is: *to reliably collect data while minimising the required floor-space and hence the trial's invasion into the day-to-day operation of the ICU.*

3.3 Computer Requirements to operate CURE Soft

CURE Soft started as several MATLAB codes that performed both data acquisition and computation (Redmond et al., 2014a; Davidson et al., 2014). In early 2014, CURE was updated into CURE Soft (Szlavec et al., 2014), an executable Java program that could run on any Java supported device: a phone, tablet, or computer. However, serial communication necessary with the Christchurch Hospital's Puritan Bennett PB840 ventilators is much easier with a computer and the simultaneous data acquisition and computation is too complex for phones and tablets (refer to Section 3.6.3). The schematic process of the application of CURE soft is shown in Figure 3.4.

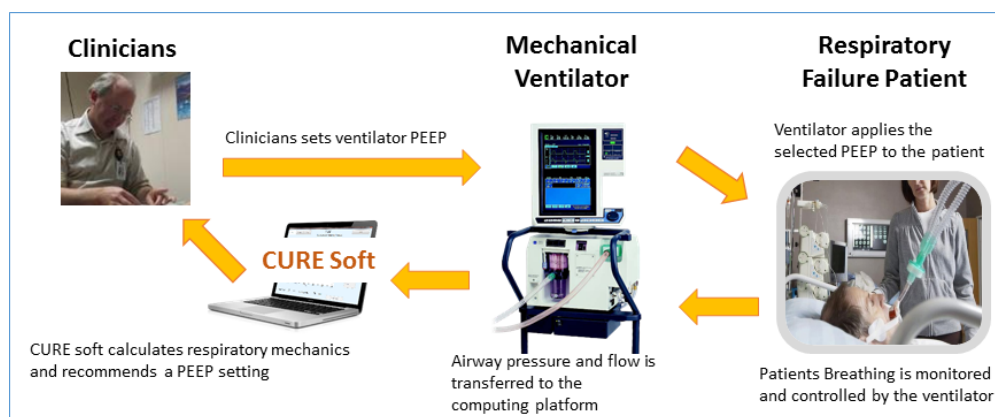


Figure 3.4. Clinician interaction with the ventilator, patient and CURE Soft.

CURE Soft was written for use with Windows 7. Unfortunately, universality is not possible due to the different methods of serial communication used by different operating systems. Although Ubuntu was briefly explored as a possibility, Windows 7 was chosen for simplicity as a requirement, as well as because of its ubiquitous usage. Windows 7 is also FDA approved as a platform adding weight to future possibilities. Any Windows 7 computer with adequate performance to run CURE Soft would suffice, but there are additional physical and abstract requirements and wishes for the CURE hardware. The graphical user interface of the CURE Soft is shown in Figure 3.5. The user guide can be found in (Szlavec et al., 2014).

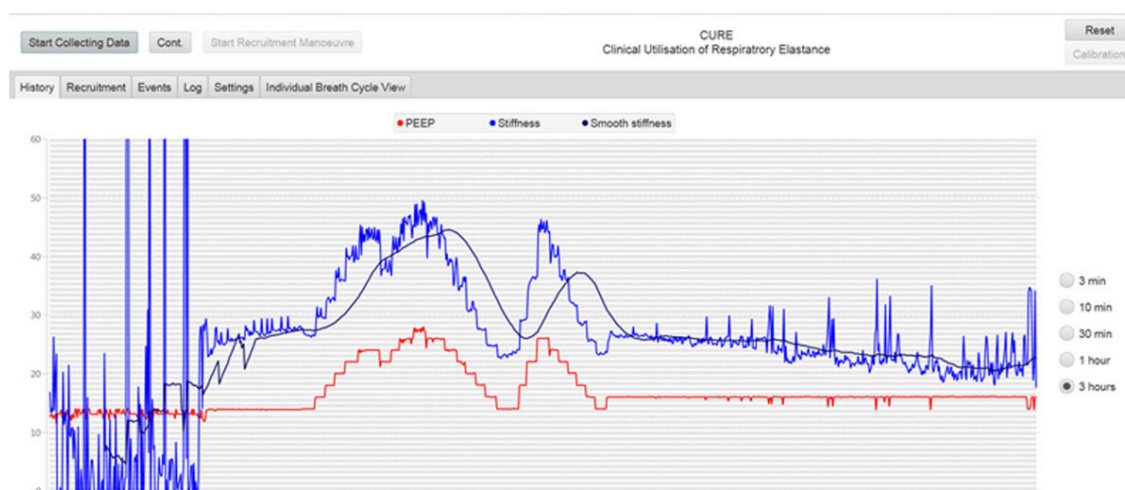


Figure 3.5. An illustrative section of clinical data used for software testing (Szlavec et al., 2014).

3.4 Hardware Specifications

There are two components necessary for the CURE RCT hardware: a computer and a monitor. Products that combine the two exist, but the requirements of each component need to be considered. The fundamental specifications for the hardware were simple: a computer with sufficient performance and a touchscreen monitor, yielding:

1. Random access memory: At least 4 GB RAM - 4 GB would be low and considering the low price of RAM, 8 GB was preferable.
2. Processor: At least Intel i5 processor or equivalent - Intel i3 Celeron for example is inadequate for the real-time continuous data acquisition and computing necessary to run CURESoft.
3. Operating system: Windows 7 - CURE Soft was developed for Windows platform.

4. Universal serial bus: At least two USB ports and preferably at least one USB 3.0 port - CURE Soft requires one port for serial communication with the ventilator, another to retrieve data (USB 3.0 preferably) and possibly another one port for monitor power and touch (depending on chosen monitor).
5. Cooling capacity: Excellent cooling capacity - Acknowledging the real-time continuous data acquisition and computing involved in CURE Soft, the generally warm environment of the ICU (~18-20°), and the need to operate uninterrupted for potentially weeks at a time, it is crucial that the computer and monitor can operate in these conditions. (Refer to Section 3.6.3 for exploration of cooling in a Microsoft Surface Pro 3 and an Intel i5 NUC.)
6. Monitor for graphical user interface: Monitor size (> 12 in.) and resolution (> 1024 × 768): Since the user must be in close proximity to use the touchscreen, adequate size and resolution is necessary for both aesthetics as well as detailed and accurate touch use.
7. Device lifetime of at least 3 years: CURE RCT is expected to run for 3 years and the hardware should not have to be replaced before the end of the trial.
8. Mass and size: The hardware should not be bulky or heavy to ease the hardware mounting discussed in Section 3.8.
9. Aesthetics and professionalism: Acknowledging that CURE RCT will be running for three years in the ICU while being visible to patient families and ICU staff while representing both the ICU and UC, it is paramount that the hardware must be aesthetically professional to ensure that users and patient families can have confidence in our work.

Other common computer specifications that need to be considered when comparing similar computers were also identified and include:

1. Solid state hard-drive (SSD) compared to hard-disk drives (HDD): SSDs have advantages over traditional HDD including improved durability to shock, operating quieter, being more lightweight, requiring less power while staying cooler and overall improvements in speed.
2. Graphics card: This computer will not be used to run graphics intensive programs so high performance graphics cards are not a requirement.
3. Wireless chip: The computer does not need to be connected to the internet during use. The necessary install processes can occur using a network port.

3.5 Computing and Display Hardware Choices

As previously mentioned, the computer and monitor could be independent devices or combined in one device. Four types of devices were considered:

1. All-in-one PC
2. Windows 7 Tablet PC (e.g. Microsoft Surface Pro 3)
3. Laptop PC
4. Mini PC with monitor

These four categories of devices are vastly different with respect to the number of available products and their specifications. The following detailed outline shows the description of each devices and their corresponding advantages and disadvantages.

1. All-in one PC

- 1.1. These devices integrates all computational components into one case.
- 1.2. Advantages: They are relatively simplistic and portable compared to a full desktop.
- 1.3. Disadvantages: All of the all-in-one PCs on the market in March 2015 were either: 1) reasonably low specified with only 4 Gb RAM, i3 or i5 processors (e.g. the Hewlett-Packard range), or 2) overly specified towards graphics and overly expensive (e.g. the iMac range).

All-in-ones have large screen sizes to accommodate desktop use and as a result, all of the options found were very large and heavy, most around 8 kg¹, would be clunky in the bed space and without a rear mount would be very difficult to mount on or near the ventilator.

Concerns were raised about the cooling capacity of these kind of machines. Most are designed to be sleek with very few cooling vents.

2. Windows 7 Tablet PC

- 2.1. A lightweight, portable device running Windows 7 in a tablet form – keyboardless.
- 2.2. Advantages: The main benefit of using a tablet is their small weight with a perfect sized screen with no unnecessary peripherals.

¹ <http://all-in-one-pc-review.toptenreviews.com/>

2.3. Disadvantages: Most tablets lack the performance to run CURE Soft but those that can lack sufficient cooling capacity to maintain operation for days or weeks at a time. Further detail is included in Section 3.6.3.

3. Laptop PC

- 3.1. A lightweight, portable device running Windows 7 with the inbuilt keyboard.
- 3.2. The main appeal of laptops is that they are lightweight, complete machines that are available in a range of performance specifications and screen sizes.
- 3.3. The keyboard component of laptops contain the processing components of a computer (otherwise it would be classified as a tablet) but the keyboard is not a major part of the use of CURE Soft. Keyboards are a major concern of the ICU's technicians as they are very difficult to maintain sterile. The keyboard also makes mounting the laptop on or near the ventilator difficult.

Considering these first three devices, there was no machine on the market that fulfilled all of the required computing hardware specifications. Our solution was to construct a machine with exactly the specifications desired consisting of a mini PC with an attached touchscreen monitor.

4. Mini PC with monitor

- 4.1. A mini PC is a miniature desktop unit approximately 4x4 inches, not designed for portability and does not include any peripherals and must be paired with a monitor.
- 4.2. One benefit of using a 'mini' PC with a touchscreen monitor is the freedom to choose the specifications best for this application and the freedom to mount the components as we wish. The computer can be built to order with exactly what CURE Soft requires and paired with a monitor perfect for the clinical application.
- 4.3. The drawbacks of the mini PC and monitor option is the price – despite the computer itself costing less than a similarly specified laptop, the additional cost of an operating system and an external touchscreen monitors add to the expense.

3.6 Selecting a Tablet PC and mini PC for testing

In this study, after evaluating the pros and cons of each PC categories, two devices were selected for the CURE Soft testing. They are a tablet PC and a mini PC. These devices are selected based on the advantage of portability with adequate performance

3.6.1 Tablet PC

The emerging consumer market of Tablet PCs is fast-changing and new technologies result in more powerful tablet PCs that are increasingly rivalling laptops. The Microsoft Surface Pro 3 is a high performing, compact device. The Surface Pro 3 is available in an option with 8 GB of RAM, a 1.7 GHz Intel i7 processor, and 512 GB of memory and in theory would be more than suitable for CURE Soft implementation. However, with the extremely compact design of the Surface Pro 3, cooling may be an issue when operating in a 24/7 high intensity data acquisition and processing mode. A cooling test was performed with a Surface Pro 3 and is included in Section 3.6.3.



Figure 3.6. Microsoft Surface Pro 3².

3.6.2 NUC mini PC.

In March 2015, there existed a diverse range of mini PCs from makers including Gigabyte³, Lenovo⁴, Asus⁵, and Intel⁶. Mini PCs are often marketed as perfect for video conferencing or

² http://www.microsoftstore.com/store/msusa/en_US/pdp/Surface-Pro-3/productID.300190600

graphic design applications. Importantly, the power and sophistication of these machines easily rivals modern high-end laptops.

The Intel Next Unit of Computing (NUC) was selected for a test platform and it could be sourced from a local supplier (Dove Electronics, a local wholesale IT distributor⁷), which simplified the overall procurement process. Dove Electronics can source the NUCs barebones or assembled with componentry. The computing hardware requirements were easily met by selecting a Dove Electronics product with 8 GB of RAM, 256 GB SSD, a 5th generation Intel Core i5 processor with a Windows 7 license. The box itself has four USB 3.0 ports, uses low power and voltage at 65W and 18V, which is ideal for the ICU. Intel makes most of the componentry and sells the barebones PC with assurance that the NUCs will not have cooling issues in a high intensity application. The inclusion of a SSD will also help maintain acceptable temperatures. An Intel NUC was subject to the same cooling test as the Microsoft Surface Pro in Section 3.6.3.



Figure 3.7. Intel NUC mini PC⁸.

3.6.3 Heat testing of Microsoft Surface Pro versus NUC.

An Intel i5 powered Microsoft Surface Pro 3 was tested by running CURE Soft with previously obtained data. The software Cool Temp⁹, a free program utilising the inbuilt

³ <http://www.gigabyte.co.nz/products/list.aspx?s=47&ck=104>

⁴ <http://shopap.lenovo.com/nz/en/desktops/thinkcentre/tinys/>

⁵ https://www.asus.com/nz/Commercial_Desktops/Mini_PC_Products/

⁶ <http://www.intel.com/content/www/us/en/nuc/overview.html>

⁷ <http://www.dove.co.nz/>

⁸ <http://www.intel.com/content/www/us/en/nuc/nuc-board-dn2820fykh.html>

⁹ <http://www.alcpu.com/CoreTemp/>

processor digital thermal sensor, was used to monitor the temperature of the computer processing unit (CPU) during continuous data monitoring and processing.

After 2 ½ hours the CPU core temperature of the Surface Pro 3 rose to an alarming 81 °C, illustrated by Figure 3.8, at which point testing was stopped. Tablets are not designed for continuous use, especially data acquisition and real-time calculation, both of which are arduous on the machine. The i5 powered Microsoft Surface Pro 3 is one of the greatest specified machines available in early 2015, but fails to sufficiently cool itself in this application.

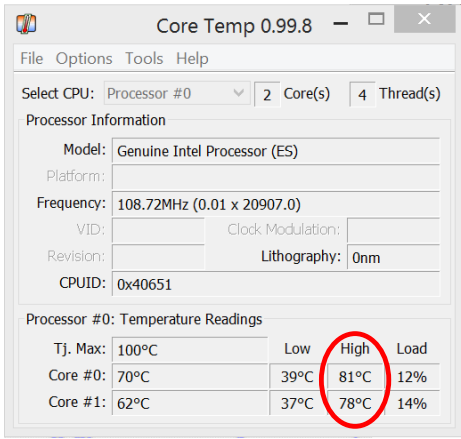


Figure 3.8. Maximum core temperature of a Microsoft Surface Pro 3 after operating CURE Soft for 2 hours.

An Intel i5 powered NUC was conducted to the same testing procedure and ran continuously for 4 days and never exceeded 66 °C as described by Figure 3.9.

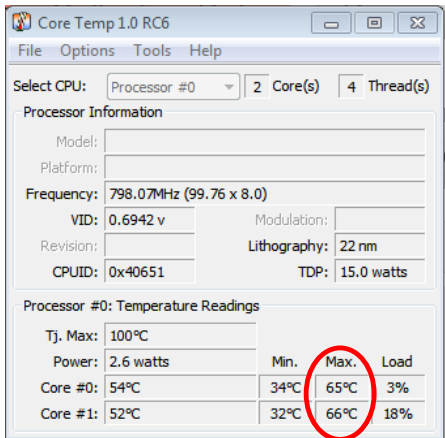


Figure 3.9. Maximum core temperature of an Intel NUC after operating CURE Soft for 4 days.

The poor cooling capability of the Microsoft Surface Pro 3 was evident when compared to the Intel NUC. Despite the on-paper specifications of the two devices being identical, as of early 2015 tablet PCs are not a viable solution for CURE hardware. However, the Intel NUC is acceptable. The Intel NUC that was purchased as a prototype for cooling testing was also used to aid design of a hardware mount.

3.7 Monitor Selection

Using a touchscreen eliminates the need for traditional peripherals such as a keyboard and mouse. However, the additional technology comes with an added cost. Use of CURE Soft requires mostly clicks or touches with minimal typing. Implementing use of a keyboard with touchpad disproportionately weights the importance of the keyboard, while adding complexity. A touchscreen monitor allows use of the pop-up on-screen keyboard, which can be closed when not in use, maintaining the full screen-size during the majority of use. Furthermore, a touchscreen enables quick and easy touch use of the software while standing close to the monitor, reducing the screen-size requirement.

3.7.1 Touch mode

Several different methods of tactile detection are used in touch devices. Point-of-sale (POS) machines mostly use resistive touch where any touch, by a finger or pen, can be detected, but requires an aggressive touch and has poor optical quality (Walker, 2012). Personal devices such as phones, tablets and laptops usually use capacitive touch, which is more sensitive to touch, but relies on the finger to alter the projected capacitive field for detection (Walker, 2012). Gloved fingers may not work with capacitive touchscreens. The Puritan-Bennett ventilators use optical touch, where two beams of light are directed across the two directions of the monitor and when the light is interrupted the touch is detected.

Resistive and optical touch can only register one touch at any time, where capacitive touch monitors can commonly register multi-touch. Capacitive touch is commonly regarded as superior, especially in high-end personal devices and is the most common in the industry (Walker, 2012). Thus, capacitive touch screen monitors were considered for this study.

3.7.2 Specific concerns in an ICU environment

Devices used in the ICU needs to meet certain added and specific criteria for health and safety reasons. In particular, several requirements were outlined for this study:

1. Electrical connections

- Since options with two devices were considered, a computer and monitor, it is important to plan the methods of connecting the two devices to mains power supply. It will be desirable to use low voltage devices i.e. not regular monitors that require a standard IEC C13 mains voltage plug.
- If a non-USB-powered monitor was selected, it would need an independent power supply. Having two AC plugs into the ICU bedspace wall was undesirable (extra cables, extra intrusion into the environment etc.) and residential style double-plugs are not allowed in the ICU for electrical safety reasons. Any kind of device that would combine the power for the two devices would need to be properly insulated and checked for electrical safety.
- A USB-powered device only requires one AC plug and since the NUC is low voltage (18V after the power supply) and USB supply is 5V, there is virtually no risk of electrical shock past the standard NUC power supply.

2. Water protection, compliance with international protection (IP) marking, IEC standard 60529.

- In the ICU every mains powered device must meet the liquid ingress requirements of IPX1 of the IP code (otherwise known as Ingress Protection Marking which denotes the level of protection against intrusion by fingers, water, dust etc. The 'X' represents no specified protection against solid particles but the '1' represents protection against dripping water). Water dripping onto the device must not enter the electrical enclosure and potentially cause an electrical fault.
- Since the NUC has cooling slots on the top and bottom of the box, to assist with natural and assisted convection, a cover must be designed that allows the NUC to be slotted into place while ensuring compliance with IPX1.

3.7.3 Monitor options considered

Many possibilities were considered, including commercial panel monitors, point-of-sale (POS) monitors, replacement laptop screens, stand-alone monitors and USB powered external monitors. In summary:

- The majority of commercial and POS monitors are resistive touch and expensive,
- POS and stand-alone monitors were heavy and bulky, and
- Commercial panels and replacement laptop screens would require complicated connections into the mating computer.
- The benefit of being USB powered is that the monitor only needs to be connected to the computer thus reducing the complication of power supply.

The best option in terms of easy connection, size, weight and price were USB powered external monitors. However, all monitors were considered for preliminary selection. Within the heavily restricted desired specification range set out by the investigators and clinical end-users, only two external monitors were found that are high resolution, lightweight, and USB powered.

1. Lenovo Thinkvision LT1423p Mobile Touch Monitor

- Could be purchased online for 550 AUD
- Capacitive 13.3-inch touchscreen supporting 1600x900 resolution
- USB 3.0 connection for both power and signal.



Figure 3.10. Lenovo Thinkvision LT1423p Mobile Touch Monitor¹⁰.

2. GeChic On-Lap 1502i Touch Monitor

¹⁰ <http://shop.lenovo.com/ae/en/itemdetails/60ACUAT2EU/460/2D2E6910F1B64671956D698D3C85F912>

- Could be purchased online for 400 USD
- Capacitive 15.6-inch touchscreen supporting full HD 1920x1080 resolution
- USB connection for power and touch but requires second HDMI cable for video.



Figure 3.11. GeChic On-Lap 1502i Touch Monitor¹¹.

3.7.4 Selecting the monitor

For a comparable price, weight and ease of mounting the GeChic 1502i was selected for the marginally larger screen-size, the wide 16:9 aspect ratio and the higher resolution. One 1502i was procured as a prototype for testing and mounting design purposes.

3.8 Mounting the Computing Hardware

Per the design goal to minimise intrusion into the ICU environment, the computing hardware needs to be mounted to allow easy use of the touchscreen, prevent cases of knocks or drops, and run the essential cables as simply and elegantly as possible.

3.8.1 Mounting concept and key factors

In a typical ICU bedside, there are various medical equipment used. Thus, there is a limited space for the inclusion of a new monitoring tool. After evaluating the bedspace area, the

¹¹ <http://www.icitouchtech.com/#!/product/prd13/1734051055/gechic-1502i-15.6%22-portable-touchscreen-monitor>

hardware was mounted directly to the Puritan Bennett 840 ventilator. Key factors in the mount design process were identified:

1. Modification of the ventilators was not allowed – any attachments to the ventilator must use pre-existing brackets, holes etc.
2. Any kind of commercial arm would need to be modified to attach to the ventilator.
3. The number of computer units will be small (6 or 8) to minimise costs but, there are more ventilators in the ICU than this so the mounting should not have to be permanent to certain or all machines.
4. Simplicity is crucial to minimize weight and cost.

3.8.2 Commercially available mounts

Most of the available monitor mounts are designed to support large TVs or monitors and usually mount to a desk, wall or ceiling. Monitors and TVs are commonly compatible with Video Electronics Standards Association (VESA) 75 or 100 consisting of four impeded threads in the device's housing for use with standard mounts. The Intel NUC also utilises VESA 100 by supplying a compatible mounting bracket which once attached secures the NUC. Ideally, this monitor mount will be able to support the monitor while also incorporating the existing NUC mounting plate. Unfortunately, neither the Lenovo or GeChic external monitors are compatible with VESA, so a mounting bracket had to be custom designed to support the monitor.

3.8.3 Simple custom mounting systems

Several mechanical design were considered. In particular, the hardware can be mounted to the side of the ventilator, hidden away behind the ventilator, and pivoted out for use, as illustrated by sketch in Figure 3.12. The ventilator itself is a tall, wheeled machine consisting of the main, functional body topped with a monitor. The ventilator chassis has very few available options to support mounting a device. One available mounting location utilised an existing mounting point on the right handrail. Unfortunately, the mechanics of a pivoting or folding arm add unnecessary weight and complexity to the mount design.

The major drawback with the general 'pivot-out from the side' concept from a structural perspective is the moment arm produced by the cantilevered weight and the lack of rigid connection points capable of transferring a moment. The pivoting action adds a great deal of

complexity to the design, as well as additional failure points. Positioning the monitor at the side of the ventilator also makes it very susceptible to knocks and collisions.

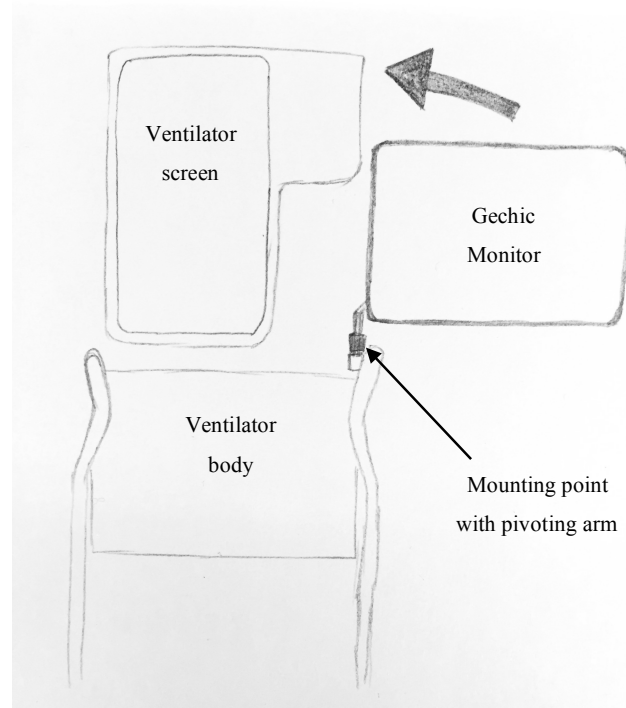


Figure 3.12. Conceptual sketch of the pivot-out concept design.

A much simpler mounting method is to place the monitor above the ventilator monitor, which practically is easy to use, adds zero extra foot-print and allows the use of a simple vertical mount greatly reducing the acting moment. Originally, a simple five legged stand (analogous to an office chair) was considered. This design can be wheeled into place behind the ventilator and does not attach to the ventilator at all, except for the RS232 data connection, as sketched in Figure 3.13. The main drawback of the wheeled concept is the instability during aggressive touching or bumping which may knock the entire stand over and damage the equipment.

A slightly more complex, but more robust, deviation on the vertical mount concept is to utilise the rear chassis member of the ventilator as the base of the vertical mount. A straight vertical pole from the ventilator chassis would place the mount stem slightly behind the ideal location which can be rectified with a small cantilever at the top to position the monitor. A concept sketch is shown in Figure 3.14. This concept was further developed and prototyped.

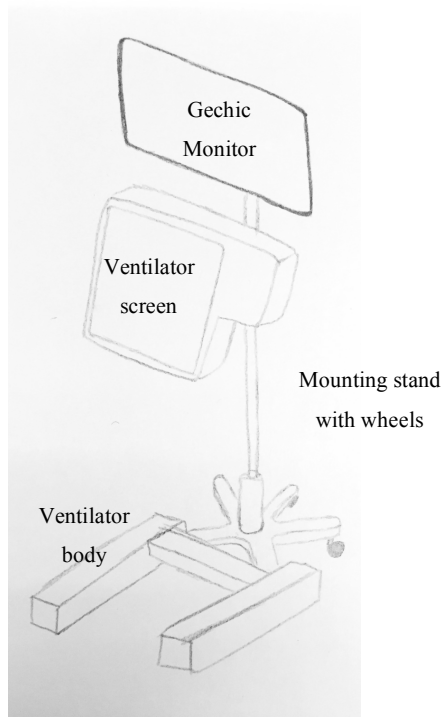


Figure 3.13. Conceptual sketch of the wheeled concept omitting the ventilator body for clarity.

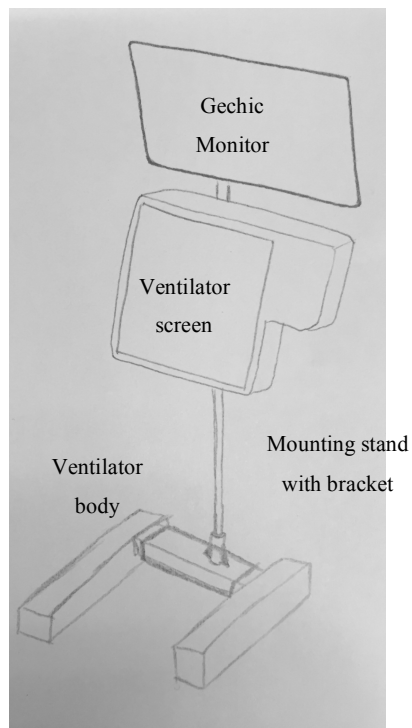


Figure 3.14. Conceptual sketch of ventilator chassis mounting design omitting the ventilator body for clarity.

A basic design consisting of three separable components was proposed. Figure 3.15 shows the Mounting design prototype. The prototype can be separated into 3 major components:

1. Monitor and computer mount
2. Upright stem
3. Chassis mount

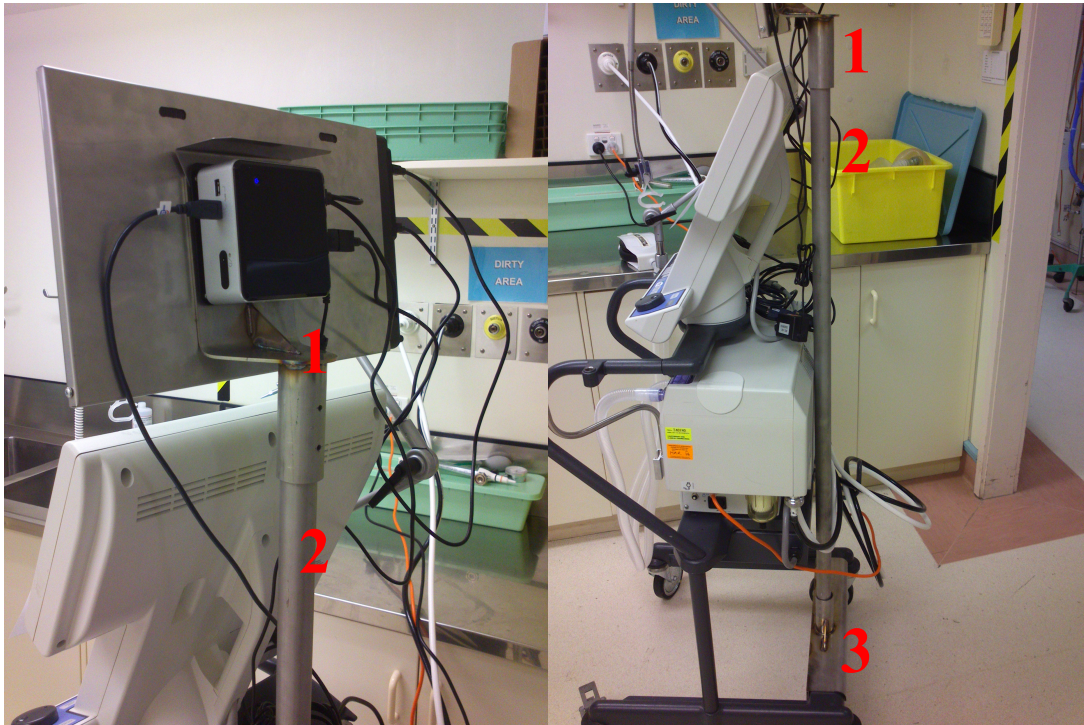


Figure 3.15. The three components of the mounting stand prototype.

Inspecting the ventilator legitimised this concept above the others with a few fortuitous coincidences. The rear chassis has an odd cross-section but does house two finger screws originally designed to secure the optional air compressor, which is never used in Christchurch Hospital ICU since compressed air and oxygen is supplied via wall outlets. These screws allow easy, fixed attachment without added brackets or cost. If the upright tubing is centred on the flat portion of the chassis member, then the pole will narrowly but perfectly miss any obstacles on the way past. Care will need to be taken to position the pole slightly off centre to the user's right hand side to avoid the cabling hook on the rear of the ventilator unit box.

3.8.4 Prototype mounting design

The design is summarised:

1. Chassis mount
 - 1.1. A 'n' shaped plate that mates over the existing ventilator rear chassis member located laterally with the two finger screws (¼" UNC thread) which also locates a larger boss welded vertically onto the flat plate with two triangular ribs for support (refer to appendix A).
2. Upright stem
 - 2.1. A 1.3 m length of tubing which transfers the loading of the hardware into the ventilator chassis (refer to appendix A).
3. VESA mount
 - 3.1. Another boss locating on the upright stem and a bent sheet that locates the monitor forward of the centre of the upright and tilted slightly down to face the user.
 - 3.2. To secure the Gechic 1502i monitor, a sleeve will encase the monitor. The monitor would need to be secured in all three directions. Gravity pulls the monitor down and forwards, due to the incline, which must be resisted. The front of the monitor must be secured at both the top and bottom to prevent any movement and at least one side must locate the monitor sideways.

Fortuitously, the Gechic 1502i has two M4 threads at the bottom of each side to be used for mounting and locating purposes. Since the plugs are accessed from the left hand side panel any component must leave this area open. An enclosure that closes around three sides of the monitor and leaves the left hand side open, was pursued. Since the entire left side is open, the monitor is simply slid in and out of position and affixed to the sleeve by a screw on the right hand side. More complicated designs could enclose the monitor on the fourth side but would require sliding or folding open and shut to place the monitor inside.
 - 3.3. To meet the IPX1 requirements, a simple component with one 90° fold was designed to be mounted with the top two VESA holes and fold across to cover the NUC like an awning.
 - 3.4. These three components will be permanently fixed as one subassembly.

The parts were modelled in SolidWorks Education 2015 to assemble with the known dimensions of the ventilator. Discussion with the Clinical Engineers of the Christchurch

Hospital suggested that stainless steel is the material of choice for its anti-corrosion and sanitation properties as well as its strength and appearance. For the chassis mount and rib components, sheet of thickness 3 mm was initially used to be strong enough for the application, the upright pole and bosses specified from schedule pipe, and 0.5 mm sheet for the 1502i sleeve and IPX1 cover.

3.8.5 Loading paths

Neglecting self-weight to start, the only load is gravity acting eccentric from the upright stem centre by approximately 100mm. The combined weight of NUC and monitor, considerably rounding up for the self-weight of the VESA mount component, is approximately 30N. The eccentric loading of the upright will introduce bending and axial loading into the VESA mount that will be transferred vertically through the upright and into the chassis mount and the ventilator chassis, as diagrammed in Figure 3.16.

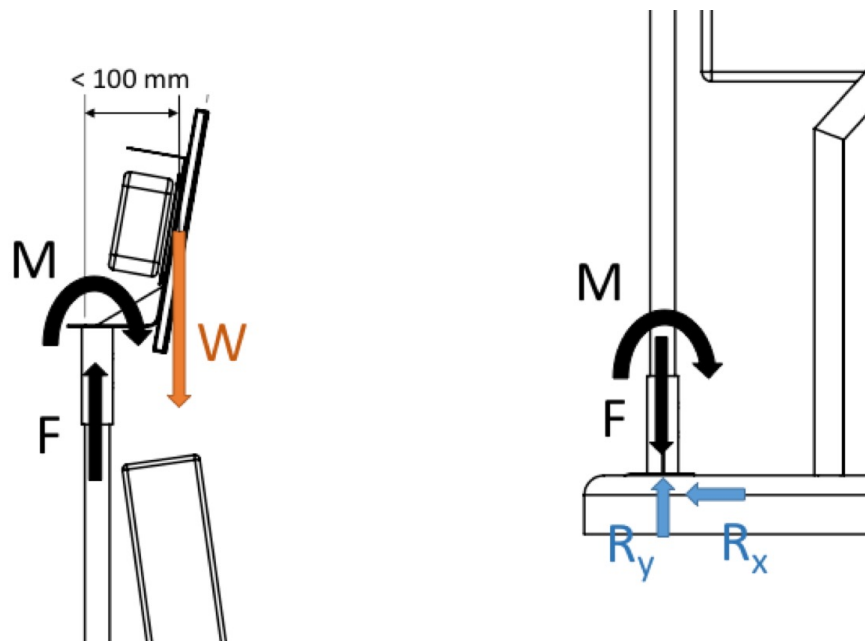


Figure 3.16. Eccentricity of loading and loading paths.

3.8.6 Prototype manufacture

The component .dxf files were sent to external contractors, ProMetal Industries¹² for laser cutting as the 3 mm 302 stainless steel sheet would be very difficult to cut precisely in the university workshop. Both the VESA mount and the chassis mount components require a radius bend. The smaller bend of the VESA mount was achieved in the small press at UC, but after some discussion the chassis mount was sent back to ProMetal for bending. Unbeknown at the time of first ordering the prototype material, ProMetal Industries performs laser cutting, folding/bending, welding and other fabrication services and would be perfect to fabricate the final design all in-house. To weld and assembly the components quickly, a private external welder Mr. Russell Major completed the welding and the assembly was finished off ready to take into the ICU for proof-of-concept testing and design consideration. Figure 3.15 shows the mounting prototype.

3.8.7 Prototype testing

The prototype was tested in the ICU and set up with a ventilator connected to a training lung (Michigan Instruments, Dual Adult Test Lung, Grand Rapids, MI). The prototype fit well against the ventilator chassis. The stand was further secured to the ventilator with an elastic tie, for security and seismic resistance as shown in Figure 3.17.

¹² <http://prometal.co.nz/>



Figure 3.17. Elastic tie restricting the movement of the prototype.

3.9 Final Mount Design

The prototype feedback from end user, the clinicians and ICU Bioengineer, and the ICU Technician team were very positive, and further modifications based on the prototype were made. The prototype was incredibly overdesigned. The 3 mm stainless sheet and the schedule pipe was excessively strong and heavy for the application. After more detailed calculations and the assurance that the ventilator box will help stabilise the upright, different material choices were made for the final design specifications. Furthermore, several minor changes were made to the design. The final product was sent to commercial fabrication company ProMetal for fabrication.

3.9.1 Detailed calculations.

Knowing the final dimensions and the masses of the hardware components, detailed calculations were completed. The weight force acting at the top of the upright stem was estimated at 35 N, and including self-weight 45 N at the base. Checking the critical force required for worst-case ($n=0.25$) buckling estimated,

$$F_{critical} = 1860\text{ N} \gg 45\text{ N}.$$

The normal stress created by the axial load was calculated to be $\sigma_{normal} = 0.5\text{ MPa}$. However, since the gravity load acts eccentric to the centre of the upright stem at a distance conservatively estimated at $e = 0.1\text{ m}$. The vertical force induces a moment creating a bending stress estimated at $\sigma_{bending} = 6.6\text{ MPa}$. Combining the normal and bending stresses results in a maximum compression stress of $\sigma_{max} = 7.1\text{ MPa}$ and maximum tensile stress of $\sigma_{max} = 6.1\text{ MPa}$. Thus, the final design will be more than adequate to support the mass of the touchscreen monitor and the NUC.

3.9.2 Procurement Costs

A budget of \$15,000 was set to procure the necessary computers for the CURE RCT. Procurement costs were accrued for purchasing components and materials for the prototype and the final purchase of 8 computing platforms and mounts. The total cost was \$14,050.21. A breakdown of the associated costs is given in Table 3.1.

Table 3.1. Confirmed final procurement costs.

Confirmed Final Procurement Costs						
Item	Item No.	Supplier No.	Qty	Supplier	Shipping	Cost
Intel NUC plus SSD and RAM	D54250WYKH	NUC287	1	Dove Electronics	\$ 4.00	\$ 757.00
Win 7 Home Premium		PC063	1	Dove Electronics	\$ 4.00	\$ 145.00
GeChic 1502i	1502i		1	ICI TouchTech	\$ -	\$ 676.07
Laser Cut parts	Quote 13582		1	ProMetal Industries	\$ -	\$ 60.00
SS tube order			1	S&T Stainless	\$ -	\$ 77.05
Intel NUC plus SSD and RAM	NUC515RYH	NUC293	7	Dove Electronics	\$ 8.00	\$ 5,460.00
Win 7 Home Premium		PC063	7	Dove Electronics	\$ 4.00	\$ 973.00
25mm SS handrail tube			2	S&T Stainless	\$ 23.63	\$ 64.23
GeChic 1502i	1502i		7	ICI TouchTech	\$ -	\$ 3,872.81
ProMetal	Quote 13727		8	ProMetal Industries	\$ -	\$ 1,760.00
Customs entry service	INV60577		-	Anglo Pacific Int.	\$ -	\$ 90.00
75x50 Timber, 5.6m lengths			2	Placemakers Ric.	\$ 40.00	\$ 31.42
Total						\$ 14,050.21

3.9.3 Final Engineering Drawings

Figure 3.18 shows the final product developed for CURE RCT. The system is attached to the ventilator, the top most screen is CURE Soft and the lower one is the ventilator. The final engineering drawings for the hardware mounts are included in Appendix A.



Figure 3.18. Final design of mounting stand mounted to a ventilator.

3.10 Chapter Summary:

In summary, to implement CURE Soft in the upcoming randomised controlled trial, an appropriate computer hardware was necessary. To minimise footprint and intrusion into the busy ICU, a hardware system comprising of a tiny PC, a touchscreen monitor and a simple stainless steel stand was devised. A prototype was produced and tested in the ICU and with positive feedback several changes were made before a total of eight units were procured. The total cost of prototype and eight units was \$14,050 within the specified budget of \$15,000. In the next chapter, retrospective analysis of the ICU data were carried out. These analyses were able to provide unique insight to the potential patient cohort that were eligible for the trial, and hence, allow better understanding and trial planning. Specifically, 8 hardware units were procured based on a utility analysis that was carried out in the next chapter.

4.0 Retrospective Analysis of ICU Patient Data

Data derived from retrospective cohorts provides important information on the current state of care, the cohort, and its response to treatment. This information can also be used to aid future planning of clinical resources and clinical practice as well as to design a clinical trial (Mantel and Haenszel, 1959). In this study, we investigated ICU patient data from a single centre, Christchurch Hospital. Data were collected from 2011 – 2014, a four year cohort of 5176 patients.

Three important metrics were studied: 1) length of mechanical ventilation; 2) risk of death; and 3) readmission rate. These three metrics can assist planning of the CURE RCT to determine the necessary recruitment rate, the required number of computing platforms, and the baseline mortality and readmission rates before the CURE intervention. The last of these points can be used to evaluate well-powered stopping criteria.

4.1 Determining the Required Number of Hardware Units

4.1.1 Introduction

The CURE RCT is a clinical trial investigating the performance of a model-based method in guiding mechanical ventilation PEEP (MBV) compared to the current standard practice (SPV) of the participating hospital, Christchurch Hospital. MBV aids clinicians in selecting PEEP using computer software, CURE Soft. CURE Soft is installed in a dedicated computing platform developed for the application, as presented in Chapter 3.

The participating hospital adult intensive care unit (ICU) is an 18 bed tertiary affiliated ICU. Ideally, one CURE computing platform would be set up for each bed for the duration of the trial. However, not all patients admitted to the ICU need invasive MV. Thus, there is no need for 18 computing platforms as they may not be fully utilised, and reducing the number of units will reduce the operation cost of the planned clinical trial.

In this section, retrospective use of the mechanical ventilation from Jan 1st 2011 to Dec 31st 2014 is studied. This study will provide information on how many patients were eligible for the CURE RCT and the number of computing platforms required can be safely estimated. It

assumes the retrospective cohort is comparable to the cohort captured by the study. Furthermore, this utility analysis will highlight any major seasonal effects that may have been overlooked during the initial trial design stage.

4.1.2 Methods

Based on the sample size analysis in Chiew et al. (Chiew et al., 2015b), a strict and objective patient selection criteria is implemented using the Acute Physiology and Chronic Health Evaluation diagnostic code (APACHE III). These objective criteria are capable of creating a simulated patient cohort based on objective criteria that could be exactly matched by the actual patient cohort, negating any subjective choices or effects. Table 4.1 shows the comparison between the actual trial inclusion and exclusion criteria versus the simulation of objective selection criteria. In addition to these selection criteria, patients with LoMV of more than 28 days were also excluded for the analysis to achieve a cohort that is shorter tailed, and thus matches the CURE trial design as well.

Table 4.1. Trial inclusion and exclusion translated into retrospective analysis.

Trial Inclusion/Exclusion Criteria		Simulation selection method
Inc.	Patients requiring invasive MV.	Only patients with recorded invasive MV are selected from the data pool.
Exc.	LoMV expected to be < 24 hours.	Excluded patients with recorded LoMV < 24 hours and all patients with APACHE III codes within groups 100 and 1200 (non-operative and post-operative cardiovascular diagnoses).
Exc.	Patients with measured or suspicion of raised intracranial pressure.	Excluded patients with APACHE III codes within the groups 400 or 1500 (non-operative and operative neurological diagnoses) as well as 601 or 1601 (non-operative and operative head trauma with or without multi trauma).
Exc.	Spinal cord injury patients.	Excluded patients with APACHE III codes 604/1604 (non-operative and operative multi trauma with spinal injury) and 605/1605 (non-operative and operative isolated cervical spine injury).
Exc.	Asthma or chronic obstructive pulmonary disease (COPD).	Excluded patients with non-operative asthma or COPD using APACHE III codes 206 (COPD) and 209 (asthma).

*See Appendix F for a summarised description for the APACHE III Diagnostic code.

After imposing the selection criteria, the remaining patient data captures the length of mechanical ventilation distribution profile for patients expected to benefit from the intervention and who will enter the trial as described in Figure 4.1. Using the patient date and time of invasive ventilation, when it started and finished, the expected number of patients requiring MV at any given hour can be calculated. Resolution of one hour was used and expected to be adequate. An example is shown in Figure 4.2.

Resolution of one day is too large as a patient will be weaned from MV and the equipment will be cleaned and may be introduced to a new participant later that same day. Resolution finer than one hour is an unnecessary complexity, especially considering the time delay for cleaning that must occur between participants. The start time was rounded down and the end time rounded up to account for these unproductive delays.

In addition, this analysis reflects the process that would occur within the ICU. If a patient enters the ICU and is eligible for the trial, but there is no computing platform available at that time, they cannot be included in the study. These patients will be missed opportunities to collect data and as such should be minimised by ensuring sufficient computing platforms are available. However, an excess of platforms will be a wasted cost. The hardware utility will be estimated as the proportion of hours where the platforms are in operation.

4.1.3 Results and discussion

Using the selection criteria, the number of eligible patients over four years was reduced to 645, with median LoMV of 4.6 days [Interquartile range (IQR): 1.9-14], with a total of 6200 days of ventilation. Figure 4.1 describes the distribution of LoMV data for the refined cohort. An estimate of the number of patients recruitable for CURE RCT is calculated and the results are shown in Figure 4.2 by months (1-48). Extrapolating the sample cohort can aid estimating the number of CURE computing platforms required.

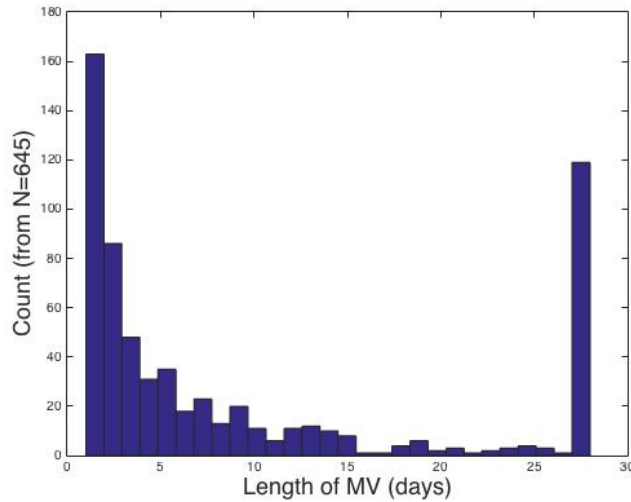


Figure 4.1. Length of mechanical ventilation distribution after sample selection.

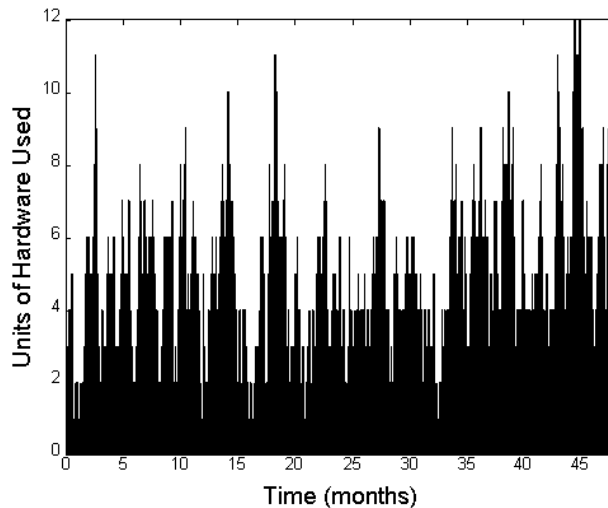


Figure 4.1. The number of hardware units required to follow each of the 645 patients, for their entire length of ventilation.

As Figure 4.2 illustrates, to collect data from every one of the 645 patients eligible for the trial, a total of 12 hardware units would be required. However, 12 units are only necessary for three hours throughout the four year period. The utility of procuring 12 hardware units would be 29%, and on average almost two-thirds (71%) of the hardware units would be unused at any time. Thus, the utility is defined as the percentage of time the units are being used to collect data. From Figure 4.2, the black shaded area is time where the hardware is being used and the white is underutilised time so the utility is calculated as the percentage of black shaded area within the total area.

In this simulated cohort, it was observed that 119 eligible participants required MV for 4 weeks. Thus, these types of patients would also occupy a unit of CURE hardware for a long time with little added benefit. An improved strategy would stop collecting data from these long-term MV participants after 10 or 14 days and free the hardware for a newly recruited participant. This strategy would still seek patients likely to benefit, but would also reduce costs, while preserving the number of participants. It also allows more participants to be recruited in a shorter time period for the same number of hardware units.

If only 5, 6, or 7 units were procured, they would, on average, be operating for a greater proportion of time. Using a maximum data collection limit of 10 or 14 days will be explored with 5, 6, or 7 hardware units. If a patient is ventilated for more than 10 or 14 days, the hardware will be removed and made available to newly entering participants. However, if fewer units are available then some patients entering the ICU may not be able to be included in the study, as there would be no currently available hardware units. The number of missed patients and the utility of each of the six cases is presented in Table 4.2 and Figures 4.3a-4.3.f.

Table 4.2. The six cases comparing the number of missed patients and hardware utility.

No. of Machines	10 days max.		14 days max.	
	Missed patients (of N=645)	Utility	Missed patients (of N=645)	Utility
5	49	50%	76	56%
6	18	44%	33	50%
7	8	38%	15	44%

As illustrated in Figures 4.3.a - 4.3.f, restricting the length of data collection reduced the units required in any given hour compared to Figure 4.2. Table 4.2 and Figure 4.3 demonstrate that limiting the number of hardware units does in fact require some of the 645 eligible patients to be missed from the trial. Limiting the number of hardware units increases the hardware utility but sacrifices some patients (< 15%). However, these small missed numbers would not significantly affect trial length or the generality of the cohort. Hence, it is acceptable given the 50% reduction in computing platforms and associated maintenance.

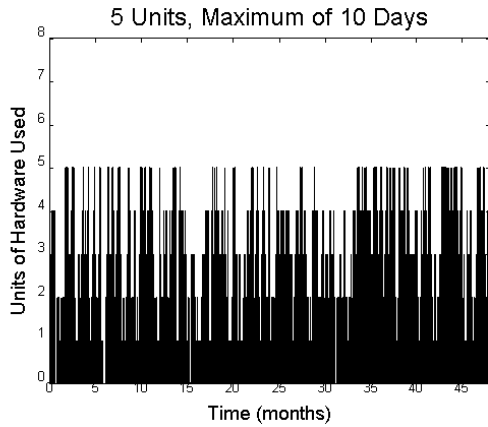


Figure 4.3.a. The number of hardware units used over four years for a maximum of 10 days and limited to 5 units.

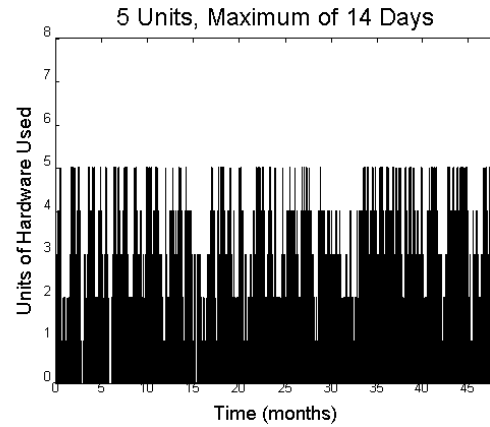


Figure 4.3.b. The number of hardware units used over four years for a maximum of 14 days and limited to 5 units.

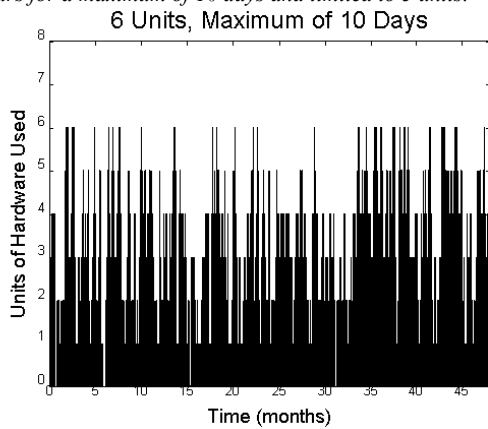


Figure 4.3.c. The number of hardware units used over four years for a maximum of 10 days and limited to 6 units.

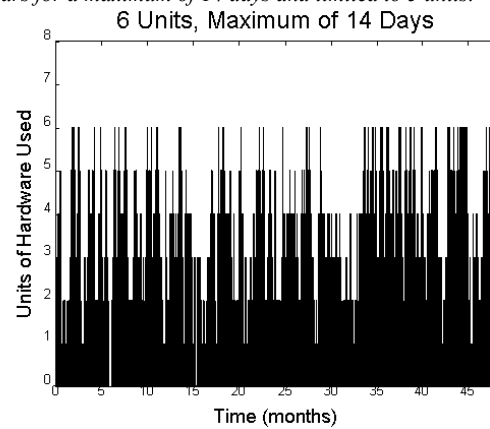


Figure 4.3.d. The number of hardware units used over four years for a maximum of 14 days and limited to 6 units.

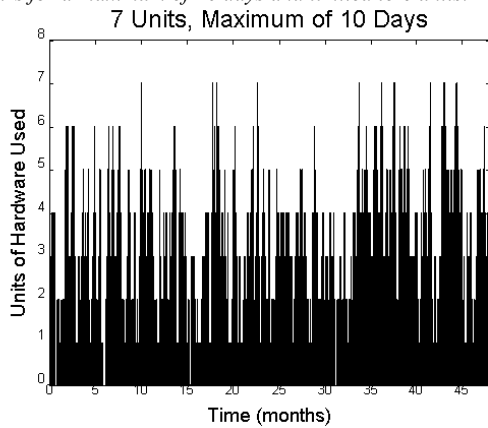


Figure 4.3.e. The number of hardware units used over four years for a maximum of 10 days and limited to 7 units.

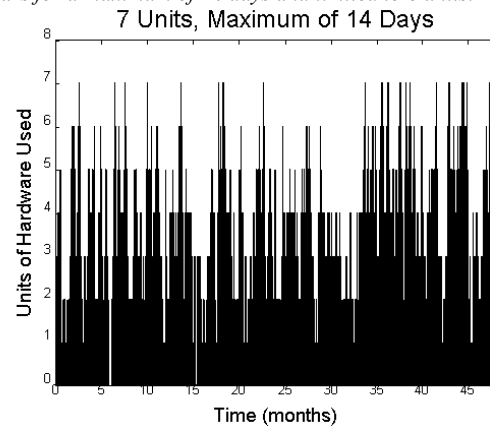


Figure 4.3.f. The number of hardware units used over four years for a maximum of 14 days and limited to 7 units.

From the results shown in Figures 4.3, there are few times where more than six units are required, but a larger proportion of times where only five units is inadequate. The estimated utility of 57% is unlikely be improved due to the large fluctuations in admissions and demand

for MV in this ICU. In addition, there is little added cost involved in having spare hardware units that are not fully utilised.

The CURE RCT plans to recruit 300 patients over two years compared to the 645 eligible in this four year analysis. The number of participants will be significantly lower during the trial, reflecting slightly stricter inclusion/exclusion criteria and any patients that drop out. Note that the trial will recruit patients under presumed consent at ICU admission with the option to withdraw later. Thus, recruitment rates are expected to be high, and there are also potential withdrawals that will lower the utility.

Based on the findings in utility analysis and collective opinion of the trial team, 8 computing platforms will be procured allowing for 2 units to be used for research purposes, while being available if any problems occur with the 6 in operation at the ICU or at times of high demand. The total cost of 8 hardware units is \$14,000, as detailed in Section 3.9.2, 56% less than 18 units based on the number of ICU beds.

4.1.4.1 Limitations and recommendations

One of the limitations of this analysis is that the patient's LoMV is aligned according to chronological order of the retrospective data. The analysis can be extended using a Monte-Carlo simulation to randomly select 300 patients from the 645 eligible patient cohort to simulate the recruited cohort. This recruited cohort is then used to inspect the number of hardware units necessary to capture each patient and thus provide a potentially more robust approximation in the utility analysis. However, this kind of simulated cohort analysis would also not be perfect as determining the recruited patients from the beginning does not reflect the daily choices in the ICU. Hence, this analysis was deemed suitable.

4.1.5 Summary: Utility Analysis

A retrospective analysis of the ICU patients admitted from Jan 1st 2011 through to Dec 31st 2014 found 645 patients would have been eligible for the CURE RCT. An hourly analysis found that for the vast majority of the time, 6 hardware units would be sufficient. However, to manage any hardware problems, 2 replacement units should be procured for research purposes and backup. Therefore, 8 hardware units will be sourced for CURE RCT.

4.2 ICU Diagnostic Codes and Estimated Risk of Death Metrics

4.2.1 Introduction

Patients admitted to the ICU are in critical condition (Marini, 2013) and commonly have respiratory failure requiring support (Marini, 2013). These patients have considerable risk of death (RoD). In particular, MV patients have typical mortality rates of 30% (Esteban et al., 2002) but patients with ALI/ARDS have mortality reported over a wide range covering 15-72% (Bersten et al., 2002; Rubenfeld et al., 2005; The ARDS Network, 2000) (Esteban et al., 2002; Zambon and Vincent, 2008). However, since 1980, ARDS mortality has been dropping from approximately 50% closer to 30% (Sigurdsson et al., 2013; Zambon and Vincent, 2008; Phua et al., 2009).

There are various metrics to quantify risk of death, for example, the APACHE II, APACHE III, and SAPS scores all have associated RoD metrics (Knaus et al., 1985; Knaus et al., 1991; Gall et al., 1984). These scores are based on simple parameters including age, body temperature, mean arterial pressure, heart rate, respiratory rate, fraction of inspired oxygen, arterial oxygenation, arterial pH, blood chemistry. They are used to broadly classify diagnosis and patient condition. This information provides prognostic value for the clinicians and they are well associated to outcome (Knaus et al., 1985; Knaus et al., 1991; Gall et al., 1984).

In this study, the risk of death metrics of the Christchurch hospital ICU are studied and compared with the actual mortality rate. This comparison investigates how well these mortality predictors perform currently to the participating hospital. In addition, retrospectively investigating mortality rates will provide insight into the expected mortality of the cohort of patients eligible for the CURE RCT. This information can be used to assist in sample size and power analysis, as well as interim and stopping rule analyses (Schoenfeld and Meade, 2004), where mortality can be used as a primary or secondary outcome.

4.2.2 Methods

Extracting all patients eligible for the CURE RCT from the 5176 patients admitted to Christchurch Hospital ICU over 4 years (2011-2014), left 645 patients. By grouping patients by Acute Physiology and Chronic Health Evaluation III (APACHE III) diagnostic code groups (100-cardiovascular, 200-respiratory etc.) and subgroups (101-cardiogenic shock, 102-cardiac arrest, 201-aspiration pneumonia, 202-respiratory neoplasm etc.), the population's

ICU and hospital mortality and risk of death (RoD) predicted by APACHE II, APACHE III and Simplified Acute Physiology Score (SAPS) scores can be directly compared. For both APACHE III diagnostic code groups and subgroups, the actual mortality rate is compared to the predicted RoDs with Pearson's correlation plot and Bland-Altman plot.

4.2.3 Results

From the cohort of 645 patients, 546 survived post ICU discharge corresponding to an ICU mortality rate of 15.4%. Compared to published mortality rates for ARDS upwards of 30% (Bersten et al., 2002; Rubenfeld et al., 2005; The ARDS Network, 2000; Esteban et al., 2002; Zambon and Vincent, 2008; Sigurdsson et al., 2013; Phua et al., 2009), the mortality of CURE RCT eligible patients is significantly lower, representing the more diverse population selected for this trial. APACHE II, III and SAPS estimate a cohort RoD of 28.0, 25.2 and 32.4%, respectively.

The group and subgroup information is illustrated in Tables 4.3 and 4.4, respectively. The three rightmost columns represent the absolute error of the estimated RoDs compared to the actual mortality. In many cases, the RoDs were significantly greater than the reported mortality for the group or subgroup. This difference is expected as the RoD metrics are created from an aggregate of data at the specific time they are constructed and may no longer be indicative of current care and outcomes.

Cells shaded green represents greater than 100% overestimation and shaded orange represents any underestimation of risk. Green cases are indicative of greater than average performance or inadequacy of the RoD measures, whereas orange cases represent an underestimation of the risk facing patients. Thus, SAPS, the oldest calibrated score has the most green cases. APACHE III generally predicts lower RoD compared to the other methods and is subsequently more accurate to the measured ICU mortality. Importantly, APACHE III is best in all of the large sampled groups.

Using APACHE II, 9 of 16 groups observed in this study had predicted mortality rate higher than actual mortality rate. 6 of 16 group had lower predicted mortality rate. Using APACHE III, 12 of 16 groups had predicted mortality rate higher than actual mortality rate with 3 lower. Using SAPS, 14 of 16 groups had predicted mortality rate higher and 1 of 16 lower than actual mortality rate.

4.2.3.1 Diagnostic code groups

Table 4.3. ICU patient information grouped by APACHE III diagnostic codes, separated into groups.

Group		Mortality (%)		APACHE II RoD		APACHE III RoD		SAPS RoD		Absolute error		
APACHE III diagnostic code	N	ICU	Hospital	median	IQR	median	IQR	median	IQR	APACHE II	APACHE III	SAPS
0	54	11%	13%	0%	0%	0%	0%	0%	0%	11%	11%	11%
200	213	21%	26%	32%	32%	29%	38%	29%	38%	-12%	-8%	-8%
300	19	32%	37%	62%	39%	52%	53%	48%	43%	-30%	-20%	-17%
500	67	22%	31%	49%	28%	44%	41%	46%	44%	-26%	-21%	-24%
600	27	7%	11%	10%	12%	9%	11%	21%	23%	-3%	-1%	-14%
700	69	4%	6%	3%	6%	8%	11%	39%	44%	2%	-4%	-35%
800	7	43%	57%	0%	0%	79%	54%	53%	54%	43%	-36%	-10%
900	5	40%	40%	34%	35%	45%	39%	77%	36%	6%	-5%	-37%
1000	2	0%	0%	0%	0%	4%	2%	8%	8%	0%	-4%	-8%
1100	3	0%	0%	42%	41%	24%	19%	41%	37%	-42%	-24%	-41%
1300	28	4%	7%	12%	8%	3%	6%	10%	17%	-8%	0%	-7%
1400	84	12%	23%	27%	28%	18%	21%	31%	32%	-15%	-6%	-19%
1600	37	11%	16%	6%	15%	4%	24%	15%	37%	5%	7%	-4%
1700	10	20%	20%	27%	20%	9%	14%	20%	16%	-7%	11%	0%
1800	2	0%	0%	32%	19%	3%	4%	6%	9%	-32%	-3%	-6%
1900	18	6%	6%	0%	0%	17%	31%	27%	39%	6%	-11%	-21%

Some interesting cases that arise in Table 4.3 include:

- Group 200, non-operative respiratory. APACHE II, III and SAPS predict 32, 29 and 29% mortality, but the actual recorded mortality is only 21%. All three metrics moderately overestimate (N=213). This group is the largest group and most likely to have ARDS and be included in the CURE RCT.
- Group 700, non-operative metabolic. APACHE II and III predict 3 and 8% RoD, but SAPS predicts 39%. Actual ICU mortality is 4% (N=69). APACHE II and III are moderately incorrect while SAPS significantly overestimates mortality and should not be used for this group.
- Group 800, non-operative haematological. APACHE II predicts 0% while ICU mortality is reported at 43% (N=7). APACHE II should not be used for this group as it may not account for factors affecting this particular subgroup.
- Group 1600, post-operative trauma. Actual mortality of 11% (N=37) is higher than predicted by both APACHE II and III of 6 and 4%. These patients may need additional care.

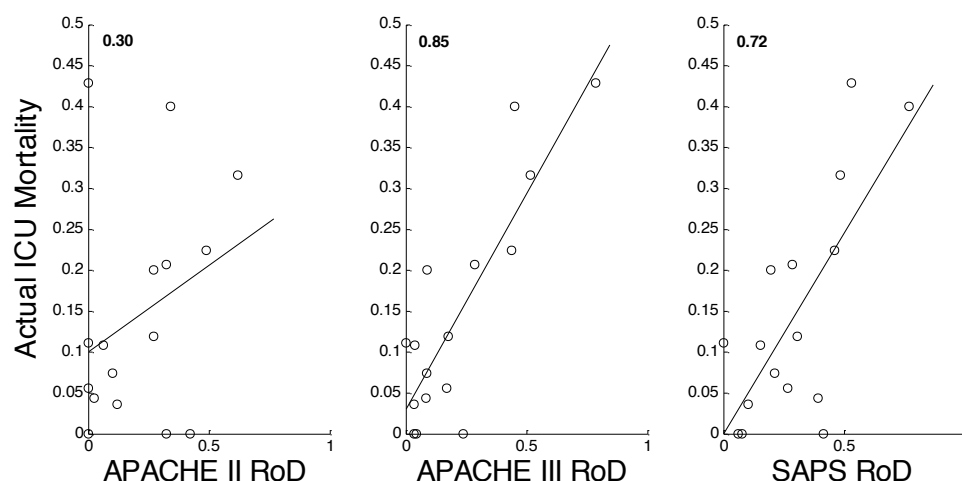


Figure 4.4. Pearson's correlation coefficient and correlation plots for group analysis.

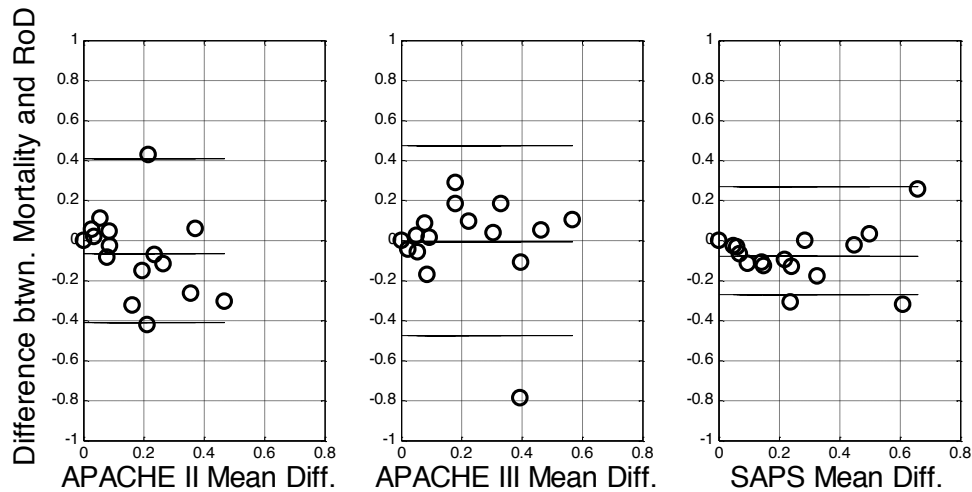


Figure 4.5. Bland-Altman plot for group analysis.

Figure 4.4 illustrates that APACHE III is the superior metric, as expected as it is the newest and updated metric, while comparing diagnostic code groups with the highest correlation coefficient of $R=0.85$ compared to 0.30 and 0.72 of APACHE II and SAPS respectively. This result aligns with literature findings, where APACHE III provides a better estimation of patient risk of death compared to APACHE II or SAPS or the newer SAPS II iteration (Reina et al., 1997; Wunder et al., 2004). Since APACHE II, III and SAPS were developed in particular sets of ICUs and published in 1985, 1991 and 1984 respectively (Knaus et al., 1985; Knaus et al., 1991; Gall et al., 1984), calibration must be performed for the individual ICU (Katsaragakis et al., 2000) after which the method's performance is more comparable (Markgraf et al., 2000; Kim et al., 2005).

Furthermore, the Bland-Altman plot of Figure 4.5 describes a zero bias of the APACHE III metric with only one instance of poor performance outside the bounds of ± 2 standard deviations from the mean. Although APACHE III has the largest bounds, likely skewed by the one outlier, the combination of greatest correlation coefficient with zero bias and acceptance variation reinforces that APACHE III is the superior metric for determining ICU RoD for a grouped cohort similar to that expected for the CURE RCT. The approach and result is thus of use when designing such a trial.

4.2.3.2 Diagnostic code subgroups

Table 4.4. ICU patient information grouped by APACHE III diagnostic codes, separated into subgroups with $N > 9$.

Group		Mortality (%)		APACHE II RoD		APACHE III RoD		SAPS RoD		Absolute error		
		ICU	Hospital	median	IQR	median	IQR	median	IQR	APACHE II	APACHE III	SAPS
APACHE III diagnostic code	N											
0	54	11%	13%	0%	0%	0%	0%	0%	0%	11%	11%	11%
201	36	14%	19%	37%	24%	25%	35%	36%	36%	-23%	-11%	-22%
203	10	10%	20%	46%	41%	37%	44%	56%	55%	-36%	-27%	-46%
208	12	33%	42%	28%	51%	19%	36%	20%	25%	5%	14%	14%
211	24	13%	13%	17%	22%	24%	25%	19%	21%	-5%	-12%	-6%
212	85	20%	27%	36%	33%	32%	43%	31%	42%	-16%	-12%	-11%
213	30	23%	27%	32%	24%	22%	27%	20%	24%	-9%	1%	3%
501	12	33%	33%	35%	38%	19%	37%	18%	53%	-1%	14%	15%
503	40	28%	40%	52%	20%	49%	28%	48%	37%	-25%	-22%	-21%
504	10	0%	0%	47%	43%	27%	28%	48%	23%	-47%	-27%	-48%
602	19	5%	11%	11%	12%	10%	11%	27%	24%	-5%	-4%	-21%
703	62	5%	6%	3%	4%	8%	10%	39%	44%	2%	-3%	-34%
1301	14	0%	0%	10%	6%	2%	2%	9%	13%	-10%	-2%	-9%
1304	12	0%	8%	15%	8%	6%	7%	15%	18%	-15%	-6%	-15%
1401	18	33%	39%	50%	22%	23%	35%	40%	34%	-16%	10%	-7%
1408	28	4%	4%	20%	29%	13%	25%	25%	33%	-16%	-10%	-21%
1602	32	13%	19%	6%	17%	5%	25%	16%	39%	6%	8%	-3%
1904	12	8%	8%	0%	0%	14%	27%	26%	24%	8%	-5%	-17%

There are several interesting cases described by subgroup results shown in Table 4.4. Presented here are those with $N > 9$ recorded cases in this analysis.

- Group 203, respiratory arrest. All three metrics significantly overestimate RoD by 27 and 46% compared to the actual mortality of 10% ($N=10$). Similarly, group 503, sepsis with shock other than urinary, a common cause of ARDS. Actual mortality is high at 28% ($N=40$), but predicted much higher at 52, 49, and 48%. These two cases may be indicative of exceptional care provided to these patients.
- Group 208, mechanical airway obstruction. All three metrics underestimate RoD by 5 and 14% compared to the actual mortality of 33% ($N=12$). Patients with this diagnosis may require additional care.
- Group 501, sepsis other than urinary. Actual observed mortality is high at 33% ($N=12$), but predicted at 35, 19, and 18%. Both APACHE III and SAPS significantly underestimates the risk to these patients, while APACHE II performs well. This could perhaps be an area for the ICU to focus on.
- Group 504, sepsis of urinary tract origin with shock. Predicted high RoD of 47, 27 and 48%, but out of the $N=10$ patients included, all survived. This may be indicative of exceptional care provided to these patients.

Similar to the overall result presented in Section 4.2.3.1 for each subgroup, APACHE III appears to be the superior estimated RoD metric. Figure 4.6 describes an APACHE III correlation coefficient of $R=0.56$ compared to 0.43 and 0.34 for APACHE II and SAPS. Figure 4.7 illustrates the slight positive bias of APACHE III compared to the larger, potentially expected negative bias of APACHE II and SAPS. Both Figures 4.6 and 4.7 include small sample size subgroups and subgroups with estimated or actual mortality of zero.

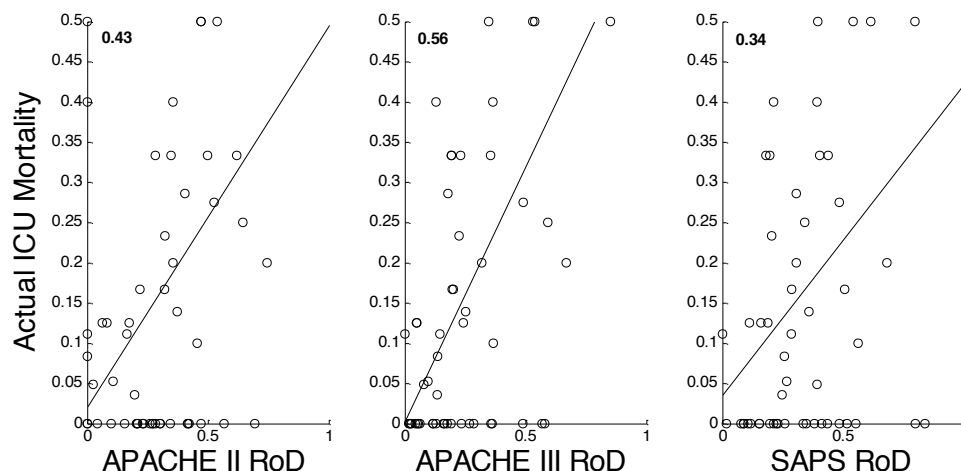


Figure 4.6. Pearson's correlation coefficient and correlation plots for subgroup analysis.

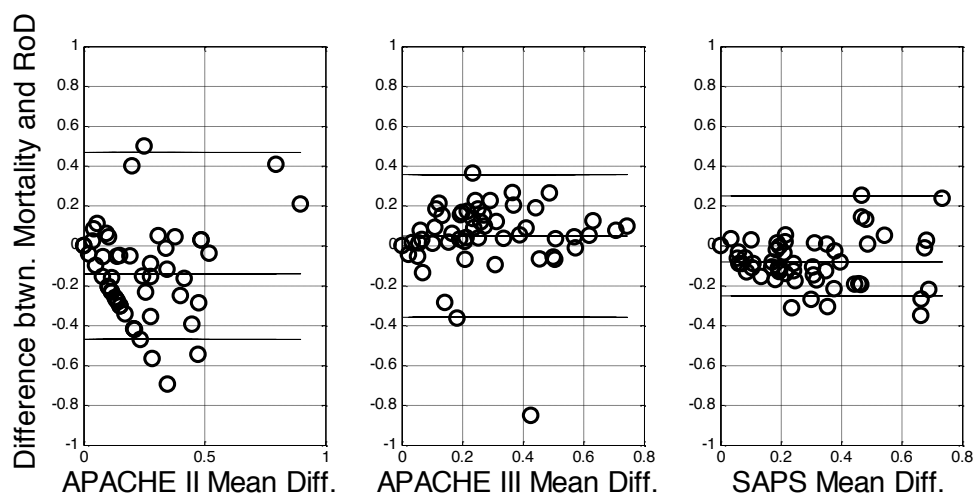


Figure 4.7. Bland-Altman plot for subgroup analysis.

4.2.3.3 Limitations

The major limitation of this analysis is assuming that every patient with an identical APACHE III diagnostic code is similar in disease severity. This assumption is unavoidable, but improved by inspecting the subgroups. However, for a large group such as 703, drug overdose, there is a very significant variation between patients in their condition and thus their real risk of death. In particular, this group contains many patients who have estimated RoDs near the combined mortality rate of 5%, but there are also outliers within the population of N=301. The RoD estimated for one particular patient is 13, 22 and 66% by APACHE II, III and SAPS respectively and another patient 0, 2 and 31%. There is thus a

huge disparity among patients and the method of pooling similar patients with a simple mean of individual RoDs may not be valid in these cases.

Figures 4.6 and 4.7 include all of the subgroups, some of which only include 1 or 2 patients, at equal weightings to those with 85 patients. A more detailed analysis could weight the patient groups and subgroups by their sample size to focus on the groups and subgroups with the most patients. Generalised RoD metrics can only provide an overall estimation of RoD and may not be specific for a single centre. However, it is found that, overall, it was able to capture the mortality rate of this participating centre relatively well with $R = 0.85$ for APACHE III.

4.2.4 Summary: RoD Analysis

It appears from this retrospective analysis of 645 ICU patients from Jan 1st 2011 to March 31st 2015, that APACHE III is the best method to assess the patient's risk of death based on their APACHE III diagnostic codes. APACHE II and SAPS are comparable over all groups and subgroups but each do perform best for specific diagnoses. However, APACHE III is not able to completely capture risk of death or cohort mortality rate of the ICU patients groups due to the variability in hospital practice, care and outcome, but can provide a good first estimate for design.

4.3 Retrospective Analysis of ICU Readmissions

4.3.1 Introduction

It was observed in the previous analyses that several of the 5176 ICU patients were readmitted into the ICU at a later date. Naturally, the length of time between admissions, as well as the first and second diagnoses differed for each patient. It was hypothesised that readmissions could be categorised and future readmissions predicted. If patients susceptible to similar readmission could be identified and the reason for reoccurring admission resolved, the demand for ICU beds and the associated cost of treatment could be reduced.

4.3.2 Methods

Patients were identified using their National Health Index (NHI) number [but could not be identified outside of research analyses] and compared to every other admission into the ICU over the 4 years from Jan 1st 2011 to Dec 31st 2014. Occurrences of the same patient being

admitted were extracted and collated. The length of time between initial discharge and subsequent readmission was calculated and used to define three categories:

1. Short-term readmissions (< 7 days): These cases are likely to be due to re-development of the initial condition or cases of complications where surgical intervention may have been required.
2. Mid-term readmission (> 7 but < 28 days): Readmissions in this category are likely to be of mixed causality.
3. Long-term readmissions (> 28 days): These cases are less likely to be direct results of the initial insult, but may represent chronic disease progression, severely ill patients in-and-out of hospital wards, or distinct illnesses.

4.3.3 Results and Discussion

4.3.3.1 Complete ICU cohort of 5176

From the 5176 patients included in this retrospective analysis, a total of 510 (~10%) readmissions were identified. From these cases, the majority were cases of a single readmission with 96 cases being a third or higher admission. Thus, 414 different patients were readmitted at some time. Table 4.5 includes the number of readmission cases for each of the three categories outlined.

To investigate each readmission separately, the diagnostic code for the first admission is compared to the second. Patients are pooled based on their APACHE III diagnostic code groups and the number of occurrences. The result is presented in Tables 4.6-4.8 for short-, mid-, and long-term readmissions, respectively.

Table 4.5. Number of readmissions in each of the three categories (N=5176).

Time before readmission	Number of readmissions
$t < 7$ days	198 (39% of 510; 3.8% of 5176)
$7 < t < 28$ days	81 (16% of 510; 1.6% of 5176)
$t > 28$ days	231 (45% of 510; 4.5% of 5176)

Illustrative example from Tables 4.6 indicated by *:

Row 400, Column 200: 8 patients are first admitted with diagnostic code of 400 and were subsequently readmitted in less than 7 days with 200 diagnostic code.

Table 4.6. Short-term ($t < 7$ days) readmissions. ($N = 198$)

APACHEIII Diagnostic Code	Second Admission															
	0	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400	1500
	0	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400	1500
First Admission																
0	4		1										1			
100		4		1	1		1						4	1	1	
200	1	1	24	1	1	1			1				1		1	
300			2	1		1								1		
400			8*		7	1							1			1
500			1		2	4										
600			2												1	
700		1	2					6		1			3			
800																
900														2		
1000																
1100																
1200		11	7	1	2	2	1	1		2			7		2	1
1300		1	5		1									1		
1400		1	5		4			2					1		13	
1500			2		3									1		
1600				1											4	
1700			1				1								1	
1800				1												
1900			2									1				2
2000																
2100																
2200																

Table 4.7. Mid-term ($7 < t < 28$ days) readmissions. ($N = 81$)

APACHEIII Diagnostic Code	Second Admission																							
	0	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2200	
First Admission																								
0	1	1												1										
100			2		1								5				1							
200			8			1			1															
300	1			1				1							1									
400		1			1											1	1	1						
500													1		1									
600		1	2																					
700			1		1			5																
800						1								1										
900																								
1000																								
1100			1																					
1200		2				3						6			3									
1300																				1				
1400		1				2							1		6									
1500			1		2									1		2								
1600															1									
1700		1						1																
1800																								
1900																								
2000																								
2100																								
2200																								

Table 4.8. Long-term ($t > 28$ days) readmissions. ($N = 231$)

APACHEIII Diagnostic Code	Second Admission																						
	0	100	200	300	400	500	600	700	800	900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2200
First Admission																							
0	7		1			1							1										
100		4	1			3		2					1	1									
200		2	42	1	1	2		1					10	2	2	1		1					
300				2					1						3				1				
400		1	4		3	1		1					1		1	1							
500		1				5		1					2		2			1					1
600	1		1		1	2		3					2	1									
700		2	2		1			13		1			2		1	1	1						
800	1							1															
900			1					1															
1000																							
1100																							
1200		2	5	1	2	2	1						15	2	3			2		1			
1300			2		1			2					1	2									
1400		3				2	1							1	7								
1500			2	1	1										3								
1600							1																
1700			1												1			2					
1800																			1				
1900			1																				
2000																							
2100																							
2200																							

As expected, there is a large spread of readmission occurrences in both axes reflecting the wide range of ailments in the ICU and reinforcing that readmissions at Christchurch Hospital are not caused by negligence in one or a few particular areas.

The following are the six most significant trends, based on the number of cases recorded with an emphasis on respiratory significance, and are outlined by colour in Tables 4.6-4.8.

1. To be readmitted into the same diagnostic code group (shaded green): This trend tends to be a significant proportion of the total sample (40%, 37% and 46% for short-, mid-, and long-term readmissions respectively).
2. To start in 200 (non-operative respiratory) and move elsewhere (shaded blue): Only occurs to small numbers, but significant to MV research (4, 2 and 10%).
3. To start in 1200 (post-operative cardiovascular) and move elsewhere (shaded yellow): Most significant for short-term readmissions (15, 10 and 9%).
4. To be readmitted into 200 (non-operative respiratory) (shaded orange): Occurs in moderate to small numbers but is significant to MV research (20, 9 and 9%).
5. To be readmitted into 1200 (post-operative cardiovascular) (shaded red): Occurs in small numbers (7, 9 and 9%) but is a major use of ICU and hospital resources.
6. To be admitted post-operative and readmitted non-operative with similar diagnosis, i.e. cardiovascular 1200 to cardiovascular 100 or respiratory 1300 to respiratory 200 (shaded purple): Most common for short-term readmissions (12, 5, and 3%) and is most likely to reflect complications post-surgery in the short-term or chronic illness in the long-term.

Tables 4.6-4.8 outline four quadrants defined by non-operative or post-operative in each axis.

1. Non-operative to non-operative (APACHE III diagnostics ≤ 1100): Contains the largest proportion of cases (41, 41 and 52%) that occur most often for long-term readmissions.
2. Initially admitted post-operative (APACHE III diagnostics ≥ 1200) and readmitted non-operative: Common to not very common (30, 16, and 13%). Most common for likely related short-term readmissions and may be caused by chronic illness or unrelated long-term readmissions.
3. Initially admitted non-operative and readmitted post-operative: Not very common but greater proportion for mid- and long-term readmissions (10, 17, and 17%), likely caused by complications or planned interventions of chronic illness.

4. Post-operative to post-operative: Common to not very common. The greatest proportion occurs for mid-term readmissions (19, 26, and 18%) which may be caused by insults that require several surgeries.

From the 5176 patients admitted to the ICU from Jan 1st 2011 to Dec 31st 2014, there were a total of 510 cases of a readmission. Only considering these 4 years of the Christchurch Hospital ICU, it can be estimated that 10% of patients being admitted would have either previously been admitted into the ICU or can be expected to be readmitted after discharge. In reality, many more patients are likely to have already been admitted and discharged from this or another ICU in previous years due to the limited time-span included in this analysis. Data from many more years and other ICUs is needed to reinforce the arguments made in this analysis.

Tables 4.6-4.8 describe the occurrences of short-, mid-, and long-term readmissions of less than 7 days, between 7 and 28 days, and greater than 28 days respectively. Tables 4.6-4.8 illustrate the basic trends of changing patient condition, pre- and post- operative admissions, and worsening chronic illness. In many cases, patients are readmitted within their previous diagnostic code suggesting the prevalence of chronic illness and return of the same or similar insult. In particular, non-operative respiratory and metabolic and post-operative cardiovascular and gastrointestinal diagnoses in all three groups, as well as non-operative neurological and sepsis diagnoses were short-term cases.

4.3.3.2 Refined CURE RCT Eligible cohort of 645

A similar analysis to Section 4.3.3.1 was conducted on the cohort of patients that have previously been used to estimate the cohort that may be enrolled for the CURE RCT. Due to the much smaller sample size of 645 only 20 (~3%) cases of readmission were observed affecting 19 different patients. In similar proportions to the larger cohort, the number of cases on short-, mid- and long-term, readmissions were 7, 3 and 10, respectively. The APACHE III diagnostic code groups for the readmissions of the smaller CURE RCT cohort are compared for short-, mid- and long-term cases as shown in Table 4.9-4.11.

Table 4.9. Short-term (< 7 days) readmissions for the estimated CURE RCT cohort.

N = 7		Second Admission		
		0	200	1900
First Admission	0	2		
	200		2	
	300		1	
	700		1	
	1900			1

Table 4.10. Mid-term (> 7 but < 28 days) readmissions for the estimated CURE RCT cohort.

N = 3		Second Admission		
		0	200	1400
First Admission	0	1		
	200		1	
	500			1

Table 4.11. Long-term (> 28 days) readmissions for the estimated CURE RCT cohort.

N = 10		Second Admission						
		0	200	500	700	1300	1400	1600
First Admission	0	1						
	200		3					
	500			1				
	700		1		1			1
	1300					1		
	1400						1	

Almost all of the cases described in Tables 4.9-4.11 are shaded green representing readmission with similar diagnosis. The three other cases otherwise are shaded orange representing a readmission into group 200, non-operative respiratory.

The readmission results for the smaller CURE RCT cohort illustrate that of the 645 patients considered to be eligible for the trial, 19 would have already been admitted and discharged from the ICU for common, similar conditions. Over the two year period expected of the CURE RCT, 9 (3% of 300) cases of readmission can be expected of patients who are eligible for CURE at both admissions. It is even more likely that recruited trial participants may have

previously been admitted and discharged from the ICU at a rate of approximately 10% or 30 during the study. There is thus little chance of a patient being enrolled twice. This information can be used to determine the inclusion and exclusion criteria of a clinical trial accounting for readmission.

4.3.3.3 Limitations

The major limitations of this early work are the lack of very long term data, the basic nature of the available data, and the grouping of patients into APACHE III groups. Being able to trace individual patients who have been readmitted to identify the reason for their readmission and whether it was clinically linked to the initial insult would add complexity to the analysis but reinforce the causal speculation included in this discussion. A more complete analysis would inspect the subgroups of patients with identical diagnoses, but would require much more data.

Readmissions are defined by a change in ICU identification number for the same NHI number. Thus, the patient must have recovered fully or improved enough to be discharged home or to another ward before being readmitted. The ICU has both acute (e.g. drug overdose, trauma etc.) and planned admissions (e.g. cardiac surgeries). It is thus likely that readmissions into post-operative codes may correspond to planned surgeries, rather than complications caused by the initial insult where the patient would not be discharged.

4.3.4 Summary: Readmission Analysis

Recording a hospital's ICU admissions is routine practice but inspection of cases of readmission is rarely performed. By retrospectively tracking readmission cases, it may be possible to forecast which patients are susceptible for short-, mid-, or long-term readmissions. The clinicians could use this information to forecast readmissions and provide sustained care or management of chronic disease to prevent patient deterioration and costly ICU readmissions. It can be expected that at least 10% of patients being admitted into the ICU have or will be admitted again and likely with a similar diagnosis.

4.4 Chapter Summary:

Three metrics were retrospectively analysed with data from Christchurch Hospital ICU from 1st Jan 2011 to 31st Dec 2014. 5176 patients were included and a cohort of 645 patients who would have been likely to be eligible for the CURE RCT were extracted. The length of mechanical ventilation was investigated to determine that 6 CURE hardware units would suffice but 8 would be procured with 2 additional units for research and backup purposes.

The estimated risk of death of the cohort was investigated against the actual mortality of 15.4% and determined that APACHE III was superior to APACHE II and SAPS. These metrics were generally able to capture RoD for this participating ICU. However, small deviations arise as standard of practice care varies from one centre to another.

Cases of readmission were investigated first, on the N=5176 cohort and second, on the N=645 CURE RCT cohort. ICU readmissions are estimated at greater than 10% however, the addition of more data will likely raise the estimate. Within the smaller CURE RCT cohort, a readmission rate of only 3% was estimated within the 4 year period. Over the course of the CURE RCT, it was estimated that only 9 occurrences of trial eligibility may be prevented by prior enrolment into the trial. This number is small and negligible but is noted and taken into account for the planned RCT.

5.0 Trial Commencement

Commencement of any randomised controlled trial (RCT) can be complicated with ethics approval, clinical protocol design, financial planning, hardware procurement, and data storage (Farrell, 1998). To date, the ethics approval and the majority of the clinical protocol design had already been completed during the ethics application process. However, it is often that during pre-trial, a minor changes in clinical protocol for example, can result in updating various documentations related to the changes.

5.1 Pre Trial Commencement

One of the main tasks before a trial commences, is the completion of the clinical training documents. To accompany the clinical protocol and CURE Soft should be a CURE RCT manual. The CURE RCT manual includes all the instructions for every aspect of the trial.

CURE RCT Manual

CURE Soft was intended for use by intensivists, registrars and attending nurses. The clinicians are qualified for their jobs, but the added burden of having to participate in a trial and learn how to use a new software could discourage some. To ease potential anxiety, it was decided to focus on software use in the documentation. A selected few people will be trained in the finer details of hardware and software setup but every clinician involved in the trial should understand how to complete a recruitment manoeuvre (denoted as max RM) and PEEP titration (denoted as PUMP manoeuvre) manoeuvre for example.

A training manual for the clinicians is attached at the end of the thesis. Please refer to Appendix B for the Training Manual. It is subject to continual changes as the research team gather feedback on the software, protocol and training documents.

5.2 CURE RCT Work-Flow

The expected work-flow of the CURE RCT trial is depicted in Figure 5.1. This work flow is generated from the perspective of an ICU patient, and is part of CURE trial RCT training.

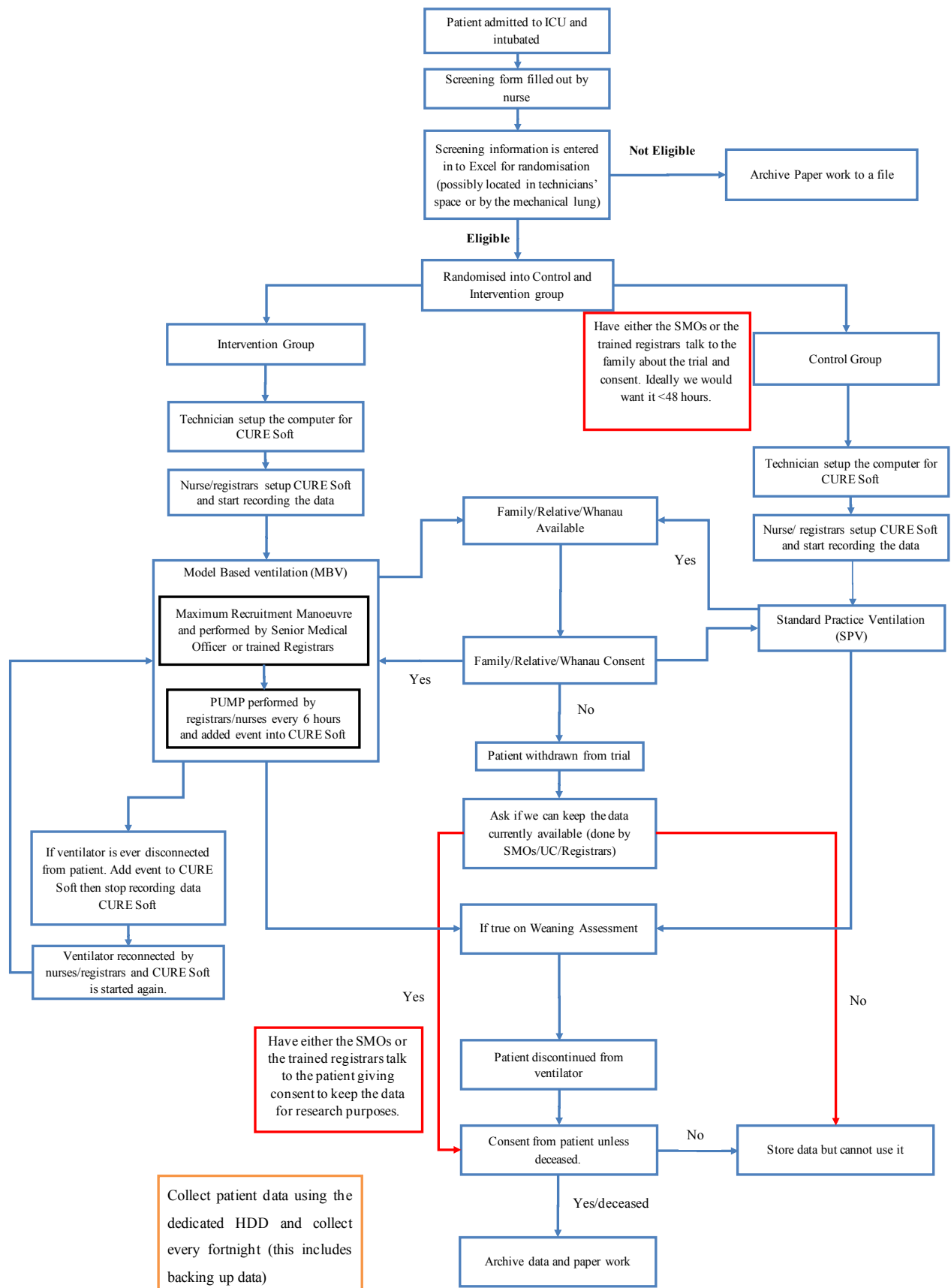


Figure 5.1. The expected work-flow diagram of the CURE RCT trial from the perspective of one patient.

When a patient is admitted to the ICU and subsequently intubated for invasive ventilation, the patient will be screened for eligibility. A nurse or attending clinicians will need to fill out a hard copy form using a patient identification label to confirm patient name, date of birth and NHI number. The information will then be transferred into an electronic database for data storage. The details of the screening sheet are shown in Appendix C.

Once the screening information has been entered into the electronic database, a randomisation algorithm assigns eligible patients into different treatment groups. In this CURE RCT study, the intervention group (MBV) and control group (SPV). A block randomisation sequence was utilised with blocks of 4, 6, and 8. The block randomisation eliminates bias (Schulz and Grimes, 2002) and is commonly recommended for RCTs over traditional randomisation techniques (Kernan et al., 1999).

Once enrolled into either treatment group, the data collection equipment will be set up and started. A CURE Soft stand will be attached to the rear of the participant's ventilator and set up to start collecting data. Setup should be performed by an ICU technician.

If the participant is randomised into the SPV group, the computer will collect data for the duration of their ICU stay up to 14 days. This group is the control group and has no additional invasion or interruption to regular care.

In contrast, if the participant is randomised into the MBV group, a MaxRM should be performed by a doctor or registrar as soon as the participant's respiratory mechanics have stabilised after muscle relaxant administration. From this point, the computer will continue to collect data and every time the patient is turned onto their back in a supine position, a PUMP should be performed by anyone trained to do so, most likely the attending nurse.

At any point from now, the informed family/relative/whanau consent process begins. The trial will be explained to the family using an official family information sheet. The patient's family will have time to think, ask questions, and discuss how they think the patient would respond after which time the family/friend consent form will be completed. If consent is not given, the patient's participation will immediately stop and if requested all data will be erased.

If family/friend consent is given, the trial and use of data will continue until any point at which consent is removed by family/friends or the patient themselves upon recovery. The family/friend and patient information sheets and consent forms are all included in Appendix

D. Completed consent forms, either accepting or rejecting consent, should be filed back into the CURE trial paperwork repository.

5.3 Data Collection and Repository

In CURE RCT, eight CURE Soft units were prepared for mechanical ventilation data collection. Each of the eight hardware units have 256 GB of storage space and in most cases, less than 250 MB will be obtained from one patient per day of ventilation. Since the CURE RCT will include 300 patients at an average length of ventilation of 2-4 days, approximately 300 GB of raw data will be recorded. Thus, the inbuilt hard-drives are more than adequate to last the entire trial if necessary.

Regardless of the capacity of the hardware, the data will regularly be collected, encrypted and backed-up on external hard-drives and in Cloud type storage to ensure the data is safe and to allow preliminary and interim analyses (Pocock, 1983; Grant et al., 2005). A portable external drive, Seagate Expansion with 1 TB of storage and a commercial Dropbox account with 1 TB of storage have been set up to be the permanent storage of CURE RCT raw data.

It is crucial that the primary investigators and statisticians can identify exactly who the data was recorded from and when exactly it was recorded. CURE Soft includes in the Settings tab the ability to adjust the file path to which the data will be saved. Within each folder are subfolders named by the computer's date and within those are raw data and processed data labelled by the computer's time. During staff/user training the concept of using the user's trial identification number, i.e. MBV-XXX or SPV-XXX, to save all of the patient data in one folder labelled with their unique identifier will be reinforced. The use of trial identifier as the first folder name will also facilitate an intuitive layout of the data archive. If a participant recovers and denies consent to use the data collected the entire folder can be easily deleted.

5.4 CURE Software Amendments

Within the course of this research project, many discussions regarding the software with ICU staff resulted in many minor and major changes to CURE Soft for improved ease-of-use for

the large expected audience. In addition, the target audience for the software had to change from primarily researchers to include ICU nurses, registrars, and intensivists.

In this study, discussion with two members of the ICU, Mr Miles Peters, a Nurse Educator, and Garry Anderson, a Senior ICU Nurse were carried out. They are the ICU team front-line that will be involved in carrying out further trial trainings to nurses. They are experienced and knowledgeable on the clinical and nursing workload. Hence, their feedback on CURE soft applicability and feasibility will be very useful for end user product design requirements. Discussion with Miles Peters and Garry Anderson yielded the following points:

1. The software needs to be intuitive and as simple as possible for everyday use. ICU nursing workload was found to be tedious work and have major impact on patients outcome (Spence Laschinger and Leiter, 2006; Sasichay-Akkadechanunt et al., 2003; Kane et al., 2007). Hence, application of CURE Soft and trial should aimed at not inducing additional burden to their clinical practice.
2. Additional one-click buttons to record clinical events. There should be some extra buttons to easily add events to the event log such as suctioning, disconnection (accidental or otherwise) and other. These buttons provides ease of recording of critical events involving/ affecting mechanical ventilation therapy, and reduce the nursing time spend on typing/ writing the events manually.
3. Conducting a PUMP manoeuvre is within the capabilities of nurses as they are responsible for a significant number of critical tasks. The current MV management practice conducted by nurses are mostly on setting FiO₂ based on desaturation events. Having the nursing to work on PUMP, which is a procedure to adjust PEEP will significantly ease the overall RCT workload needed to be conducted by the registrars.

Continual discussion with ICU clinician Professor Geoffrey Shaw yielded more detailed software changes. These changes also focused on ease of use and include:

1. Renaming specific identifiers so that the CURE Soft is more intuitive.
2. Using larger font sizes in CURE Soft for easier read and usage..
3. Include additional tabs for events selection.
4. Fixing PEEP scale to a realistic testing range.
5. Provide real-time step by step indicators/ instruction for the CURE Soft users during Recruitment manoeuvres or PUMPs.

Some of these changes are illustrated in the following figures. Figure 5.2 describes the change made to ease selection and enforce standardisation of Patient ID in the Settings Tab, which influences the saved data folder. Figure 5.3 depicts the changes made to split the old ‘Start RM’ button into three to simplify the process of conducting a PUMP and the addition of a pop-up number pad to easily type numbers such as PEEP, SpO₂ and FiO₂ rather than using the full keyboard.

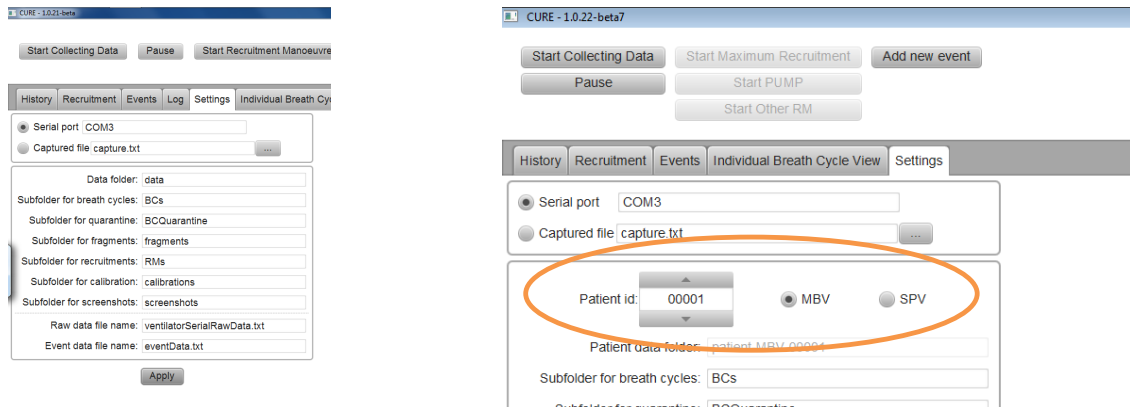


Figure 5.2. Illustrative screenshots describing the changes made to the Settings Tab.

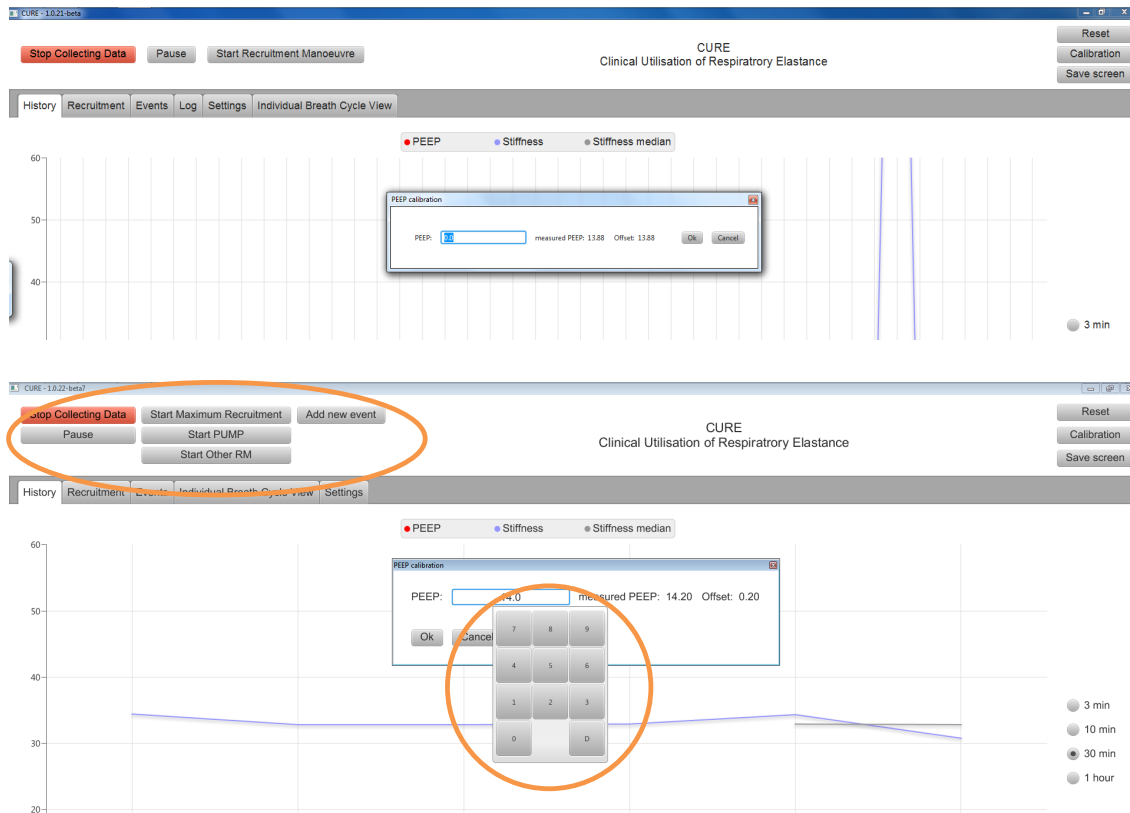


Figure 5.3. Illustrative screenshot describing the changes made to the ‘Start RM’ button and the pop-up number pad.

Figure 5.4 describes the PEEP tracker addition to CURE Soft, which simplifies the process of a maxRM or PUMP manoeuvre by instructing the user the PEEP setting to select next. The use of three columns and colour directs the user to where they may have made an error in protocol. It can also highlight, for safety, when PIP may be exceeding 55 cmH₂O.

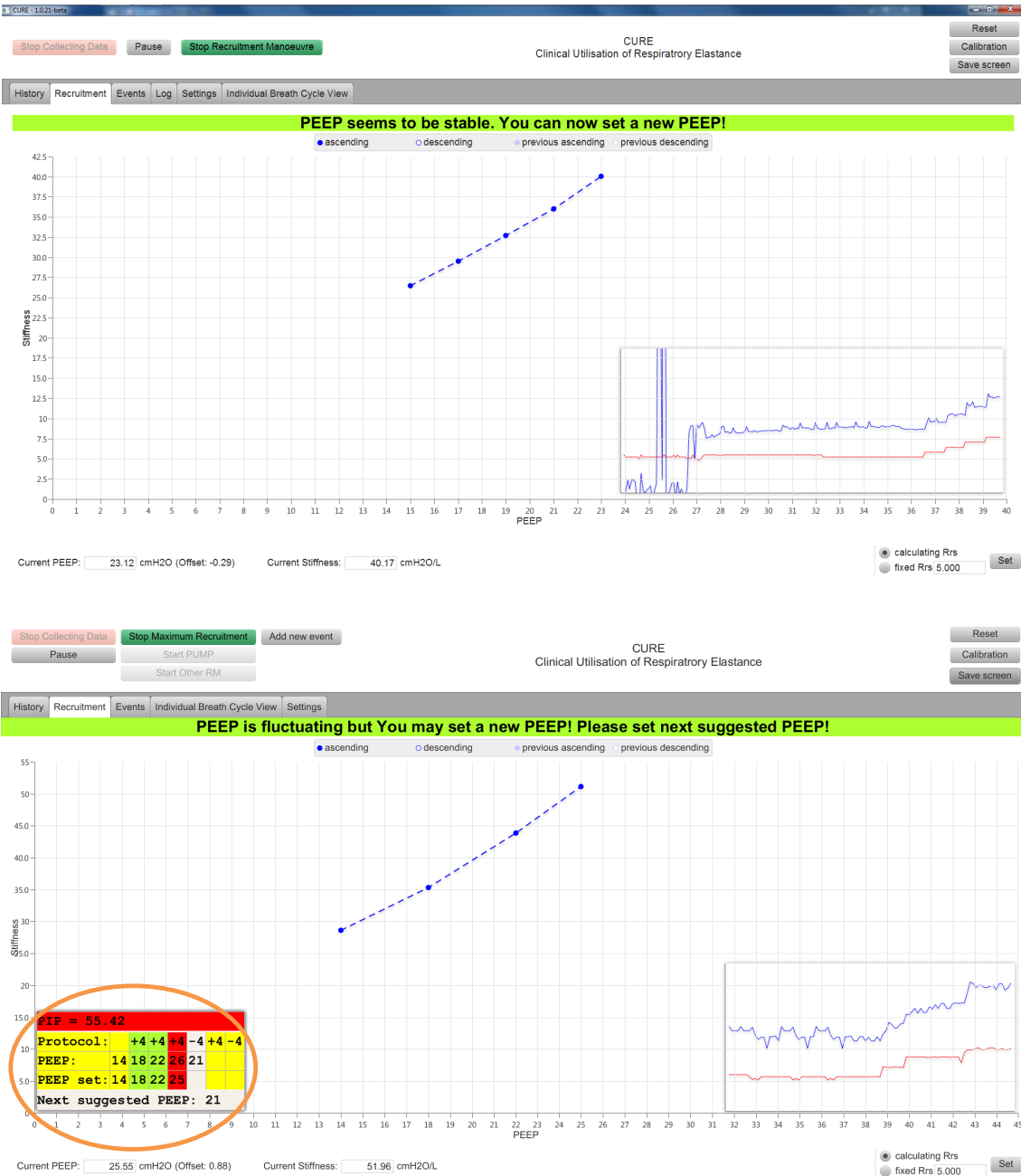


Figure 5.4. Illustrative screenshot describing the addition of a PEEP tracker.

These changes were relayed to the principle software developer Dr. Akos Szlavec who implemented them into the current CURE Soft version (Szlavec et al., 2014). Although these changes to CURE Soft interface may delay commencement of the RCT, the current version is significantly easier to use by leading the user through the steps and leaving many fewer tasks open to forget or bypass.

5.5 Chapter Summary:

Numerous aspects of documentation have been created or refined over the course of this project. These documentations and planning are necessary in order to improve the teaching of ICU staff, to manage the trial efficiently. They provide illustrations of the RCT work-flow of multiple staff members together, ensure the necessary documentation is completed correctly and to ensure the data collected is safely added to the data repository.

The software and some documentation are continuing to change and improved at the recommendations of other ICU staff. In particular, the training material is likely to evolve as more feedback and questions are received from staff progressing through training. Hence, managing this documentation is vital for a successful clinical trial.

6.0 Challenges and Future Work

6.1 Challenges Faced

Many challenges are faced as engineers trying to collaborate in medicine. For this research project the main two challenges were

1. Getting approval to incorporate the designed ICU hardware that will be used by ICU staff for a clinical trial in the indirect treatment of patients, and
2. Gaining consensus between the ICU intensivists of the fundamental theory supporting CURE in order to proceed in the study.

6.1.1 Hardware into the ICU

As previously mentioned in Chapter 3.0, the ICU has strict requirements of its equipment, and rightly so. Having to satisfy electrical safety standards is one thing, but the greater challenge was designing components to a professional standard that is intuitive and suitable for a RCT with non-engineering end-users. The final products of this project may not meet commercial standard, but the effort spent to make simple, robust, and easy to use hardware was justified and the designs should be commercialisable.

6.1.2 Intensivist Consensus

A major challenge for the clinicians, Professor Geoffrey Shaw was discussing with his peers the benefits of CURE, the details of the CURE RCT clinical protocol, and the implementation of CURE RCT. Mechanical ventilation management is challenging and with little consensus and each intensivist had their own opinion of the best ventilation strategy and compromise between peers is always difficult. Respiratory RCTs are notoriously difficult to conduct and in particular, the effect size is small compared to the number of competing factors. Thus, the CURE RCT is a bold step towards individualised patient care.

6.2 Future Work

As a result of this research project, the task of commencing the study is firmly in the hands of the clinical investigators. The necessary components have been assembled, but there remain a few more abstract hurdles to overcome. However, research is continuing with a number of

undergraduate and postgraduate students at the University of Canterbury. The main research areas are those sprouting from the commencement of CURE RCT.

6.2.1 Preliminary Analyses

Once the study commences, a steady stream of data will be collected and available for preliminary analyses. As the number of patients included increases the significance of differences in each trial outcome will improve and the efficacy of model-based ventilation will start to be assessable.

6.2.2 Virtual Patients

The CURE RCT recruits eligible patients into the trial from the start of mechanical ventilation until the end of mechanical ventilation. Thus, CURE RCT will be able to provide an unprecedented level of real-time respiratory mechanics data that can be used to track the trajectory of patients based on their ventilation therapy. Pooling data from many different patients can build an aggregated database that can be used to further inspect how different ventilation settings can affect patient condition and their end outcomes. The end goal of this kind of analysis is to identify some generalizable aspects of optimal ventilation that may not have been elucidated among the optimal ventilation debate. Further research on this area can be performed once the trial has commenced.

6.2.3 Improved Signal Processing

During the CURE pilot trials, several different branches of signal processing research have branched from the core project. It was observed that monitoring real time airway pressure and flow enables the quantification of the quality of mechanical ventilation therapy, and patient ventilation interaction. These studies found that patients exhibit ventilation asynchronies but the research was not completed prior to this project. Automated asynchrony detection (Poole et al., 2014; Chiew et al., 2015a) and waveform reconstruction (Redmond et al., 2014c; Redmond et al., 2014b; Major et al., 2016) during spontaneous breathing are ongoing research areas that will broaden the scope of CURE Soft and broaden the spectrum of eligible patients, ideally to any invasively ventilated patient. Further optimisation of these methods will be conducted with the plan to implement in successive versions of CURE Soft.

6.3 Chapter Summary:

The most difficult challenge faced in commencing the trial is the ongoing amendments made to the clinical protocol, work-flow, training strategy and CURE Soft. The amendments are created by the extensive discussion among the ICU intensivists regarding the best way to organise or run the study. The amendments are improving the documentation and software but are significantly delaying commencement. Research into mechanical ventilation is continuing at UC and the scope of the research is expanding as CURE RCT starts and new data is collected with much wider breadth and depth than available before.

7.0 Conclusions

The current standard of care in the intensive care unit regarding invasive mechanical ventilation is to follow generalised guidelines set out by the ARDS Network. These guidelines fail to consider the significant inter- and intra-patient variability associated with the respiratory system in the critically ill. During recent years, a push towards individualised patient care is revolutionising medicine but, mechanical ventilation is lagging behind. Improved monitoring of real-time, patient-specific respiratory mechanics can direct clinical professionals to select optimal ventilation settings for every patient at any time with zero additional clinical invasion.

A state-of-the-art software, CURE Soft, has been presented in previous work but an accompanying hardware system has been described in this thesis. In this study, prototype development and testing was conducted extensively and eight units were procured for implementation in the upcoming CURE randomised controlled trial. Each hardware unit accompanies a portable PC with touchscreen monitor. The unit is mounted on a stainless steel stand behind the ICU's existing ventilators to facilitate ergonomic use of the system and minimise the footprint and perceived burden of participating in the trial.

Respiratory studies are notoriously difficult to conduct with various management aspect needs to be considered. Many steps have been taken to streamline the clinical protocol and simplify the procedures necessary for the study through extensive discussions with clinicians and other ICU staff. Numerous challenges have been faced which have delayed commencement of the trial. However, this research has ensured every necessary non-clinical aspect has been organised so that the trial can commence once the clinical aspects have been confirmed. To aid the clinical discussion a thorough literature review has been conducted and presented here as a Review of Mechanical Ventilation. Every piece of critical background information can now be presented easily from one document containing many applicable references.

Retrospective analyses, using previous ICU admission data, were conducted and were able to give significant insight to the estimated patient cohort that may be enrolled into the RCT. In particular, results from these analyses contributed to planning of the RCT, such as hardware utility study, modification of CURE Soft and clinical protocol development. Future research

will likely be much broader than that possible from the limited retrospective data. Research improving signal processing and the capabilities of CURE Soft will be necessary as inevitable issues arise during the study and the large amount of data will allow researchers to create a virtual patient database where their outcome can be influenced by the respiratory therapy supplied.

With the physical resources created and refined during this research project, the primary investigators of CURE are fully equipped to commence the trial. The setbacks faced during this project have allowed for more rigorous discussion with a wider audience of stakeholders and supplied the necessary time to refine a complete set of documentation to proceed with the trial confident in our planning. Our tools and resources are easily scalable once the trial commences and the daily responsibility shifts from the primary investigators onto other trained ICU staff and if shown effective, scalable to higher powered, multi-centre studies to help transform and personalise ventilation therapy worldwide.

8.0 References

- Aboab J, Niklason L, Uttman L, et al. (2012) Dead space and CO₂ elimination related to pattern of inspiratory gas delivery in ARDS patients. *Critical Care* 16.
- Adams AB, Simonson DA and Dries DJ. (2003) Ventilatory-induced lung injury. *Respir Care Clin N Am* 9: 343 - 362.
- Adler A, Shinozuka N, Berthiaume Y, et al. (1998) Electrical impedance tomography can monitor dynamic hyperinflation in dogs. *J Appl Physiol* 84: 726-732.
- Akobeng AK. (2005) Understanding randomised controlled trials. *Archives of Disease in Childhood* 90: 840-844.
- Albert RK, Kirk W, Pitts C, et al. (1985) Extra-alveolar vessel fluid filtration coefficients in excised and in situ canine lobes. *Journal of Applied Physiology* 59: 1555-1559.
- Amato MBP, Barbas CSV, Medeiros DM, et al. (1998) Effect of a Protective-Ventilation Strategy on Mortality in the Acute Respiratory Distress Syndrome. *N Engl J Med* 338: 347-354.
- ANZICS. (2010) Centre for Outcome and Resource Evaluation (CORE) Annual Report. Victoria, Australia.
- Artigas A, Bernard Gordon R, Carlet J, et al. (1998) The American-European Consensus Conference on ARDS, Part 2. Ventilatory, Pharmacologic, Supportive Therapy, Study Design Strategies, and Issues Related to Recovery and Remodeling. *Am J Respir Crit Care Med* 157: 1332-1347.
- Bates JHT. (2009) *Lung Mechanics: An Inverse Modeling Approach*, United States of America, New York: Cambridge University Press.
- Ben-Tal A. (2012) Computational models for the study of heart-lung interactions in mammals. *Wiley Interdisciplinary Reviews. Systems Biology and Medicine* 4: 163-170.
- Bernard GR, Artigas A, Brigham KL, et al. (1994) The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 149: 818 - 824.
- Bersten AD, Edibam C, Hunt T, et al. (2002) Incidence and Mortality of Acute Lung Injury and the Acute Respiratory Distress Syndrome in Three Australian States. *Am. J. Respir. Crit. Care Med.* 165: 443-448.
- Borges JB, Okamoto VN, Matos GF, et al. (2006) Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med* 174: 268 - 278.
- Brenner DJ and Hall EJ. (2007) Computed Tomography - An Increasing Source of Radiation Exposure. *N Engl J Med* 357: 2277-2284.
- Briel M, Meade M, Mercat A, et al. (2010) Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA* 303: 865-873.
- Brochard L, Martin G, Blanch L, et al. (2012) Clinical review: Respiratory monitoring in the ICU - a consensus of 16. *Critical Care* 16: 219.
- Brower RG, Lanken PN, MacIntyre N, et al. (2004) Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. *N Engl J Med* 351: 327-336.
- Carney D, DiRocco J and Nieman G. (2005) Dynamic alveolar mechanics and ventilator-induced lung injury. *Crit Care Med* 33: S122-S128.

- Carvalho A, Jandre F, Pino A, et al. (2007) Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. *Critical Care* 11: R86.
- Chao DC and Scheinhorn DJ. (1996) Barotrauma vs Volutrauma. *CHEST Journal* 109: 1127-1128.
- Chase JG, Le Compte A, Preiser J-C, et al. (2011) Physiological modeling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice? *Annals of Intensive Care* 1:11.
- Chase JG, Moeller K, Shaw G, et al. (2014) When the value of gold is zero. *BMC Research Notes* 7: 404.
- Chiew YS, Chase JG, Shaw G, et al. (2011) Model-based PEEP Optimisation in Mechanical Ventilation. *BioMedical Engineering OnLine* 10: 111.
- Chiew YS, Chase JG, Shaw GM, et al. (2012) Respiratory system elastance monitoring during PEEP titration. *Critical Care* 16: P103.
- Chiew YS, Pretty C, Beatson A, et al. (2015a) Automated Logging of Inspiratory and Expiratory Non-Synchronized Breathing (ALIEN) for Mechanical Ventilation. *EMBC'15: 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Milano, Italy.
- Chiew YS, Pretty C, Redmond D, et al. (2015b) A better way to determine sample size to detect changes in length of mechanical ventilation? *35th International Symposium on Intensive Care and Emergency Medicine*. Brussels, Belgium.
- Chiew YS, Pretty C, Shaw G, et al. (2015c) Feasibility of titrating PEEP to minimum elastance for mechanically ventilated patients. *Pilot and Feasibility Studies* 1: 9.
- Cook DJ, Walter SD, Cook RJ, et al. (1998) Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 129: 433 - 440.
- Dasta JF, McLaughlin TP, Mody SH, et al. (2005) Daily cost of an intensive care unit day: The contribution of mechanical ventilation. *Crit Care Med* 33: 1266-1271.
- Davidson SM, Redmond DP, Laing H, et al. (2014) Clinical Utilisation of Respiratory Elastance (CURE): Pilot Trials for the Optimisation of Mechanical Ventilation Settings for the Critically Ill *19th IFAC World Congress*. Cape Town, South Africa.
- de Matos G, Stanzani F, Passos R, et al. (2012) How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography. *Critical Care* 16: R4.
- Docherty P, Chase JG, Lotz T, et al. (2011) A graphical method for practical and informative identifiability analyses of physiological models: A case study of insulin kinetics and sensitivity. *BioMedical Engineering OnLine* 10: 39.
- Dreyfuss D and Saumon G. (1998) Ventilator-induced Lung Injury. Lessons from Experimental Studies. *Am J Respir Crit Care Med* 157: 294 - 323.
- Esteban A, Anzueto A, Alia I, et al. (2000) How Is Mechanical Ventilation Employed in the Intensive Care Unit? . An International Utilization Review. *Am. J. Respir. Crit. Care Med*. 161: 1450-1458.
- Esteban A, Anzueto A, Frutos F, et al. (2002) Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. *JAMA* 287: 345-355.
- Estenssoro E, Dubin A, Laffaire E, et al. (2003) Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome. *Intensive Care Medicine* 29: 1936-1942.
- Fagerberg A, Söndergaard S, Karason S, et al. (2009) Electrical impedance tomography and heterogeneity of pulmonary perfusion and ventilation in porcine acute lung injury. *Acta Anaesthesiologica Scandinavica* 53: 1300 - 1309.

- Fan E, Wilcox ME, Brower RG, et al. (2008) Recruitment Maneuvers for Acute Lung Injury. *American Journal of Respiratory and Critical Care Medicine* 178: 1156-1163.
- Farrell B. (1998) Efficient management of randomised controlled trials: nature or nurture. *BMJ* 317: 1236-1239.
- Ferguson ND. (2012) Low tidal volumes for all? *JAMA* 308: 1689-1690.
- Ferguson ND, Cook DJ, Guyatt GH, et al. (2013) High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 0: null.
- Funk D, Graham MR, Girling L, et al. (2004) A comparison of biologically variable ventilation to recruitment manoeuvres in a porcine model of acute lung injury. *Respiratory Research* 5: 22.
- Gajic O, Dara SI, Mendez JL, et al. (2004) Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation *. *Critical Care Medicine* 32: 1817-1824.
- Gall J-RL, Loirat P, Alperovitch A, et al. (1984) A simplified acute physiology score for ICU patients. *Critical Care Medicine* 12: 975-977.
- Gama de Abreu M, Spieth PM, Pelosi P, et al. (2008) Noisy pressure support ventilation: A pilot study on a new assisted ventilation mode in experimental lung injury. *Critical Care Medicine* 36: 818-827.
- Gattinoni L. (2011a) Counterpoint: Is Low Tidal Volume Mechanical Ventilation Preferred for All Patients on Ventilation? NoLow Tidal Volume Mechanical Ventilation Counterpoint. *CHEST Journal* 140: 11-13.
- Gattinoni L. (2011b) Rebuttal From Dr Gattinoni. *CHEST Journal* 140: 15-15.
- Gattinoni L, Caironi P, Cressoni M, et al. (2006) Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 354: 1775 - 1786.
- Gattinoni L, Carlesso E, Brazzi L, et al. (2010) Positive end-expiratory pressure. *Current Opinion in Critical Care* 16: 39-44.
- Gattinoni L, Carlesso E, Cadringer P, et al. (2003) Physical and biological triggers of ventilator-induced lung injury and its prevention. *Eur Respir J* 22: 15s-25.
- Girard TD and Bernard GR. (2007) Mechanical Ventilation in ARDS. *Chest* 131: 921-929.
- Grant A, Altman D, Babiker A, et al. (2005) Issues in data monitoring and interim analysis of trials. *Health Technology Assessment* 9: 238.
- Grasso S, Mascia L, Del Turco M, et al. (2002) Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology* 96: 795 - 802.
- Guerin C. (2011) The preventive role of higher PEEP in treating severely hypoxemic ARDS. *Minerva Anestesiol* 77: 835-845.
- Habashi NM. (2005) Other approaches to open-lung ventilation: Airway pressure release ventilation. *Critical Care Medicine* 33: S228-S240.
- Hann CE, Chase JG, Lin J, et al. (2005) Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model. *Computer Methods and Programs in Biomedicine* 77: 259-270.
- Harris RS. (2005) Pressure-volume curves of the respiratory system. *Respir Care* 50: 78-98.
- Harris RS, Hess DR and Venegas JG. (2000) An objective analysis of the pressure-volume curve in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 161: 432 - 439.
- Hasan A. (2010) *Understanding Mechanical Ventilation: A Practical Handbook*: Springer.
- Hickling KG, Henderson SJ and Jackson R. (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 16: 372 - 377.

- Hubmayr RD. (2011a) Point: Is Low Tidal Volume Mechanical Ventilation Preferred for All Patients on Ventilation? Yes Low Tidal Volume Mechanical Ventilation Point. *CHEST Journal* 140: 9-11.
- Hubmayr RD. (2011b) Rebuttal From Dr Hubmayr. *CHEST Journal* 140: 14-15.
- Ionescu CM, Vandersteen G, Schoukens J, et al. (2014) Measuring nonlinear effects in respiratory mechanics: A proof of concept for prototype device and method. *IEEE Transactions on Instrumentation and Measurement* 63: 124-134.
- Kane RL, Shamliyan TA, Mueller C, et al. (2007) The Association of Registered Nurse Staffing Levels and Patient Outcomes: Systematic Review and Meta-Analysis. *Medical Care* 45: 1195-1204.
- Katsaragakis S, Papadimitropoulos K, Antonakis P, et al. (2000) Comparison of Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score II (SAPS II) scoring systems in a single Greek intensive care unit. *Critical Care Medicine* 28: 426-432.
- Kernan WN, Viscoli CM, Makuch RW, et al. (1999) Stratified Randomization for Clinical Trials. *Journal of Clinical Epidemiology* 52: 19-26.
- Kim E-K, Kwon Y-D and Hwang J-H. (2005) [Comparing the performance of three severity scoring systems for ICU patients: APACHE III, SAPS II, MPM II]. *Journal of preventive medicine and public health = Yebang Uihakhoe chi* 38: 276-282.
- Knaus WA, Draper EA, Wagner DP, et al. (1985) APACHE II: a severity of disease classification system. *Crit Care Med* 13: 818 - 829.
- Knaus WA, Wagner DP, Draper EA, et al. (1991) The apache iii prognostic system. risk prediction of hospital mortality for critically ill hospitalized adults. *CHEST Journal* 100: 1619-1636.
- Lambermont B, Ghuysen A, Janssen N, et al. (2008) Comparison of functional residual capacity and static compliance of the respiratory system during a positive end-expiratory pressure (PEEP) ramp procedure in an experimental model of acute respiratory distress syndrome. *Critical Care* 12: R91.
- Lu Q and Rouby J-J. (2000) Measurement of pressure-volume curves in patients on mechanical ventilation: methods and significance. *Critical Care* 4: 91 - 100.
- Lucangelo U, Bernabè F and Blanch L. (2007) Lung mechanics at the bedside: make it simple. *Current Opinion in Critical Care* 13: 64-72
- Major V, Corbett S, Redmond D, et al. (2016) Respiratory mechanics assessment for reverse-triggered breathing cycles using pressure reconstruction. *Biomedical Signal Processing and Control* 23: 1-9.
- Malbouisson LM, Muller J-C, Constantin J-M, et al. (2001) Computed Tomography Assessment of Positive End-expiratory Pressure-induced Alveolar Recruitment in Patients with Acute Respiratory Distress Syndrome. *Am. J. Respir. Crit. Care Med.* 163: 1444-1450.
- Mantel N and Haenszel W. (1959) Statistical aspects of the analysis of data from retrospective studies. *J natl cancer inst* 22: 719-748.
- Marini JJ. (2013) Mechanical ventilation: past lessons and the near future. *Critical care (London, England)* 17 Suppl 1.
- Marini JJ and Gattinoni L. (2004) Ventilatory management of acute respiratory distress syndrome: a consensus of two. *Crit Care Med* 32: 250 - 255.
- Markgraf R, Deutschinoff G, Pientka L, et al. (2000) Comparison of Acute Physiology and Chronic Health Evaluations II and III and Simplified Acute Physiology Score II: A prospective cohort study evaluating these methods to predict outcome in a German interdisciplinary intensive care unit. *Critical Care Medicine* 28: 26-33.

- Matthay M, Ware L and Zimmerman G. (2012) The acute respiratory distress syndrome. *J Clin Invest* 122: 2731 - 2740.
- Meade MO, Cook DJ, Guyatt GH, et al. (2008) Ventilation Strategy Using Low Tidal Volumes, Recruitment Maneuvers, and High Positive End-Expiratory Pressure for Acute Lung Injury and Acute Respiratory Distress Syndrome: A Randomized Controlled Trial. *JAMA* 299: 637-645.
- Mellemgaard K. (1966) The Alveolar-Arterial Oxygen Difference: Its Size and Components in Normal Man. *Acta Physiologica Scandinavica* 67: 10-20.
- Mercat A, Richard J-CM, Vielle B, et al. (2008) Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome: A Randomized Controlled Trial. *JAMA* 299: 646-655.
- Mertens M, Tabuchi A, Meissner S, et al. (2009) Alveolar dynamics in acute lung injury: Heterogeneous distension rather than cyclic opening and collapse *. *Critical Care Medicine* 37: 2604-2611.
- Mireles-Cabodevila E, Diaz-Guzman E, Heresi GA, et al. (2009) Alternative modes of mechanical ventilation: A review for the hospitalist. *Cleveland Clinic Journal of Medicine* 76: 417-430.
- Moloney ED and Griffiths MJD. (2004) Protective ventilation of patients with acute respiratory distress syndrome. *Br J Anaesth* 92: 261-270.
- Murphy DB, Cregg N, Tremblay L, et al. (2000) Adverse Ventilatory Strategy Causes Pulmonary-to-Systemic Translocation of Endotoxin. *American Journal of Respiratory and Critical Care Medicine* 162: 27-33.
- Mutch WA, Eschun GM, Kowalski SE, et al. (2000) Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia. *British Journal of Anaesthesia* 84: 197-203.
- Oba Y, Thameem DM and Zaza T. (2009) High levels of PEEP may improve survival in acute respiratory distress syndrome: A meta-analysis. *Respiratory Medicine* 103: 1174-1181.
- Odenstedt H, Lindgren S, Olegard C, et al. (2005) Slow moderate pressure recruitment maneuver minimizes negative circulatory and lung mechanic side effects: evaluation of recruitment maneuvers using electric impedance tomography. *Intensive Care Med* 31: 1706 - 1714.
- Parker JC, Hernandez LA and Peevy KJ. (1993) Mechanisms of ventilator-induced lung injury. *Crit. Care Med.* 21: 131.
- Parsons PE, Eisner MD, Thompson BT, et al. (2005) Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med* 33: 1-6.
- Pavone L, Albert S, DiRocco J, et al. (2007) Alveolar instability caused by mechanical ventilation initially damages the nondependent normal lung. *Critical Care* 11: R104.
- Petersen GW and Baier H. (1983) Incidence of Pulmonary Barotrauma in a Medical ICU. *Critical Care Medicine* 11: 67-69.
- Phua J, Badia JR, Adhikari NKJ, et al. (2009) Has Mortality from Acute Respiratory Distress Syndrome Decreased over Time?: A Systematic Review. *Am J Respir Crit Care Med* 179: 220-227.
- Pinsky MR. (1997) The hemodynamic consequences of mechanical ventilation: An evolving story. *Intensive Care Medicine* 23: 493-503.
- Pintado M-C, de Pablo R, Trascasa M, et al. (2013) Individualized PEEP Setting in Subjects With ARDS: A Randomized Controlled Pilot Study. *Respiratory Care* 58: 1416-1423.
- Pocock SJ. (1983) *Clinical trials: a practical approach*: Wiley Chichester.

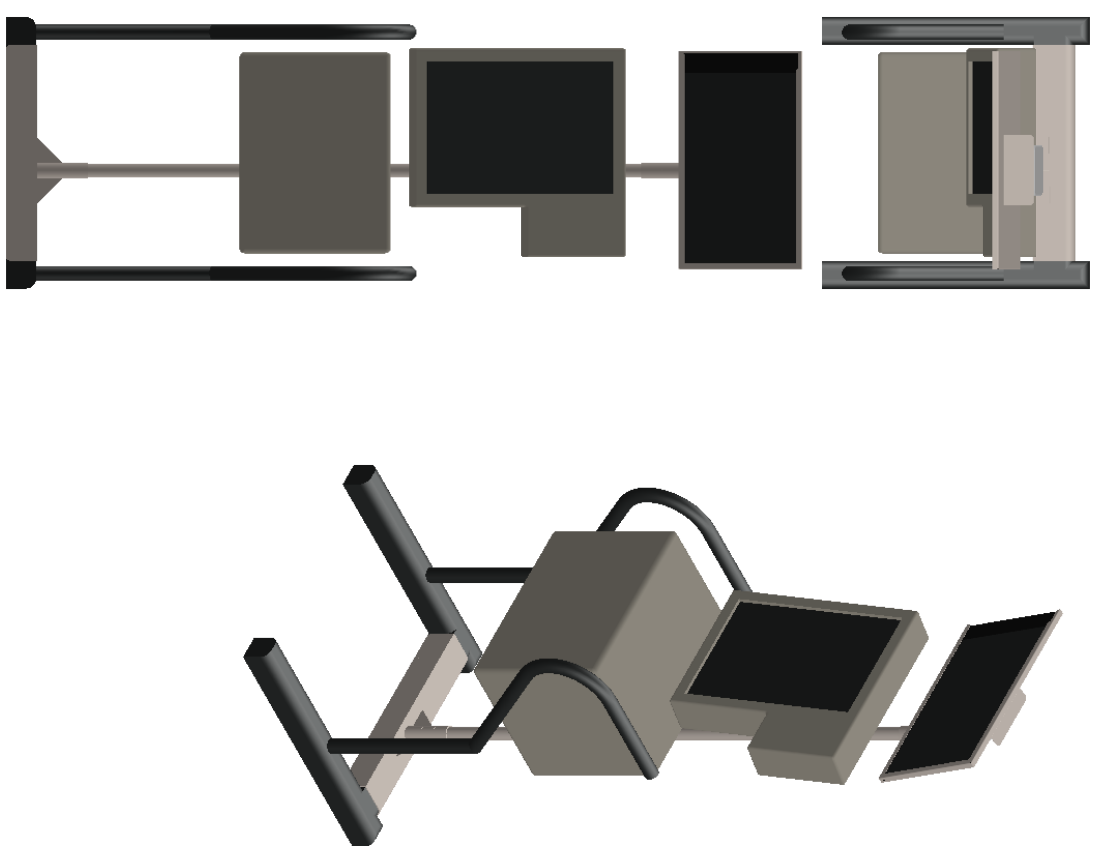
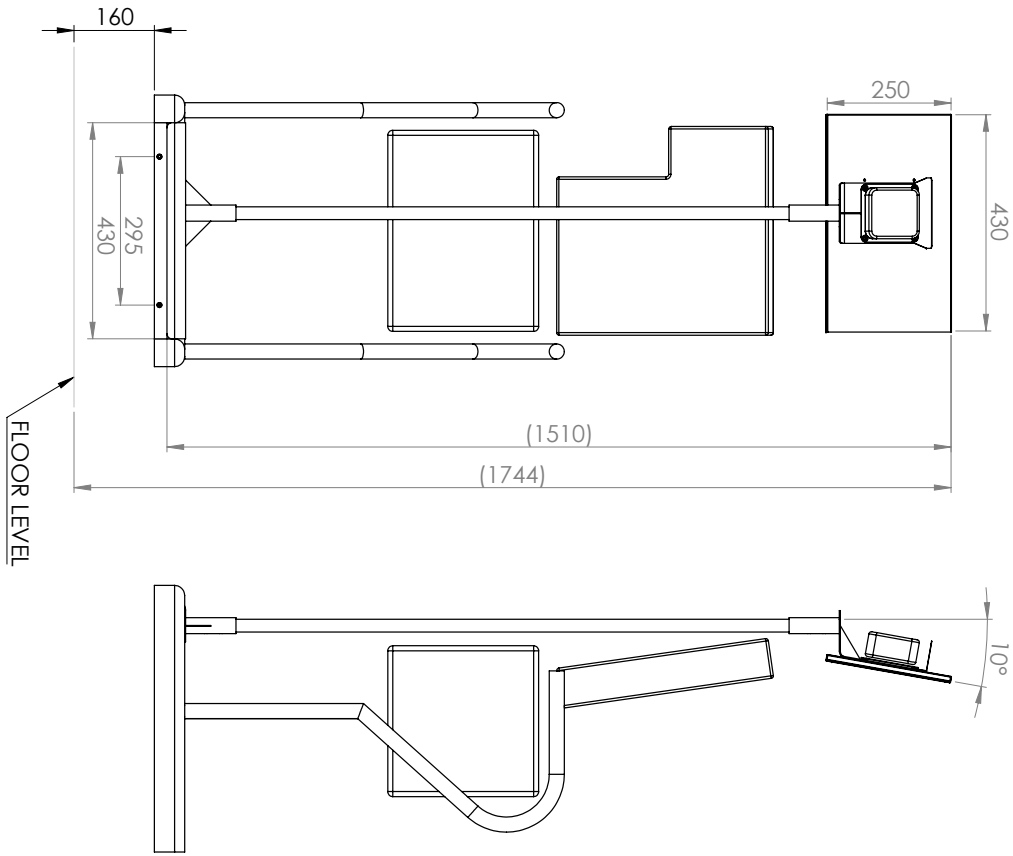
- Pomprapa A, Schwaiberger D, Lachmann B, et al. (2014) A mathematical model for carbon dioxide elimination: An insight for tuning mechanical ventilation. *European Journal of Applied Physiology* 114: 165-175.
- Poole SF, Chiew YS, Redmond D, et al. (2014) Real-Time Breath-to-Breath Asynchrony Event Detection using Time-Varying Respiratory Elastance Model. *19th World Congress of the International Federation of Automatic Control (IFAC)*. Cape Town, South Africa.
- Putensen C, Mutz NJ, Putensen-Himmer G, et al. (1999) Spontaneous Breathing During Ventilatory Support Improves Ventilation-Perfusion Distributions in Patients with Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine* 159: 1241-1248.
- Rachmale S, Li G, Wilson G, et al. (2012) Practice of excessive FIO₂ and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. *Respiratory Care* 57: 1887-1893.
- Ranieri VM, Suter PM, Tortorella C, et al. (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 282: 54 - 61.
- Rasanen J, Cane RD, Downs JB, et al. (1991) Airway pressure release ventilation during acute lung injury: A prospective multicenter trial. *Critical Care Medicine* 19: 1234-1241.
- Redmond D, Chiew YS, Van Drunen E, et al. (2014a) A minimal algorithm for a minimal recruitment model-model estimation of alveoli opening pressure of an acute respiratory distress syndrome (ARDS) lung. *Biomedical Signal Processing and Control* 14: 1-8.
- Redmond D, Major V, Corbett S, et al. (2014b) Pressure reconstruction by eliminating the demand effect of spontaneous respiration (PREDATOR) method for assessing respiratory mechanics of reverse-triggered breathing cycles. *IEEE Conference on Biomedical Engineering and Sciences (IECBES)*. Miri, Malaysia.
- Redmond DP, Major V, Corbett S, et al. (2014c) Pressure reconstruction by eliminating the demand effect of spontaneous respiration (PREDATOR) method for assessing respiratory mechanics of reverse-triggered breathing cycles. *2014 IEEE Conference on Biomedical Engineering and Sciences (IECBES)* 332-337.
- Rees SE. (2011) The Intelligent Ventilator (INVENT) project: The role of mathematical models in translating physiological knowledge into clinical practice. *Computer Methods and Programs in Biomedicine* 104, Supplement 1: S1-S29.
- Reina A, Vázquez G, Aguayo E, et al. (1997) Mortality discrimination in acute myocardial infarction: comparison between APACHE III and SAPS II prognosis systems. *Intensive Care Medicine* 23: 326-330.
- Ricard JD, Dreyfuss D and Saumon G. (2003) Ventilator-induced lung injury. *Eur Respir J* 22: 2s-9.
- Robert J. Mason, V. Courtney Broaddus, Thomas R. Martin, et al. (2010) *MURRAY AND NADEL'S TEXTBOOK OF RESPIRATORY MEDICINE*.
- Rocco PRM, Pelosi P and De Abreu MG. (2010) Pros and cons of recruitment maneuvers in acute lung injury and acute respiratory distress syndrome. *Expert Review of Respiratory Medicine* 4: 479-489.
- Rose L. (2010) Clinical application of ventilator modes: Ventilatory strategies for lung protection. *Australian Critical Care* 23: 71-80.
- Rouby JJ, Lu Q and Goldstein I. (2002) Selecting the Right Level of Positive End-Expiratory Pressure in Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 165: 1182-1186.

- Rubenfeld GD, Caldwell E, Peabody E, et al. (2005) Incidence and Outcomes of Acute Lung Injury. *New England Journal of Medicine* 353: 1685-1693.
- Rubenfeld GD and Herridge MS. (2007) Epidemiology and outcomes of acute lung injury. *Chest* 131: 554 - 562.
- Sasichay-Akkadechanunt T, Scalzi CC and Jawad AF. (2003) The Relationship Between Nurse Staffing and Patient Outcomes. *Journal of Nursing Administration* 33: 478-485.
- Schoenfeld DA, Bernard GR and Network ftA. (2002) Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Critical Care Medicine* 30: 1772-1777.
- Schoenfeld DA and Meade MO. (2004) Pro/con clinical debate: It is acceptable to stop large multicentre randomized controlled trials at interim analysis for futility. *Critical Care* 9: 1-3.
- Schranz C, Becher T, Schadler D, et al. (2013) Model-based ventialtor settings in pressure controlled ventilation. *Congress for the German Swiss and Austrian Society for Biomedical Engineering (BMT2013)*. Graz, Austria: Springer.
- Schulz KF and Grimes DA. (2002) Generation of allocation sequences in randomised trials: chance, not choice. *The Lancet* 359: 515-519.
- Sigurdsson MI, Sigvaldason K, Gunnarsson TS, et al. (2013) Acute respiratory distress syndrome: nationwide changes in incidence, treatment and mortality over 23 years. *Acta Anaesthesiologica Scandinavica* 57: 37-45.
- Slutsky A. (1993) Mechanical Ventilation. American College of Chest Physicians' Consensus Conference. *Chest* 104(6): 1833-1859.
- Slutsky AS. (1999) Lung Injury Caused by Mechanical Ventilation*. *Chest* 116: 9S-15S.
- Slutsky AS and Hudson LD. (2006) PEEP or No PEEP -- Lung Recruitment May Be the Solution. *N Engl J Med* 354: 1839-1841.
- Slutsky AS and Tremblay LN. (1998) Multiple system organ failure. Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med* 157: 1721 - 1725.
- Soo Hoo GW. (2005) Minute ventilation: It takes time to get it right. *Respiratory Care* 50: 459-461.
- Sorbini CA, Grassi V, Solinas E, et al. (1968) Arterial Oxygen Tension in Relation to Age in Healthy Subjects. *Respiration* 25: 3-13.
- Spence Laschinger HK and Leiter MP. (2006) The Impact of Nursing Work Environments on Patient Safety Outcomes: The Mediating Role of Burnout Engagement. *Journal of Nursing Administration* 36: 259-267.
- Spieth PM, Carvalho AR, Güldner A, et al. (2011a) Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. *Critical Care Medicine* 39: 746-755.
- Spieth PM, Carvalho AR, Güldner A, et al. (2009a) Effects of Different Levels of Pressure Support Variability in Experimental Lung Injury. *Anesthesiology* 110: 342-350.
- Spieth PM, Carvalho AR, Pelosi P, et al. (2009b) Variable Tidal Volumes Improve Lung Protective Ventilation Strategies in Experimental Lung Injury. *Am. J. Respir. Crit. Care Med.* 179: 684-693.
- Spieth PM, Güldner A, Carvalho AR, et al. (2011b) Open lung approach vs acute respiratory distress syndrome network ventilation in experimental acute lung injury. *British Journal of Anaesthesia* 107: 388-397.
- Stahl CA, Möller K, Schumann S, et al. (2006) Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome. *Critical Care Medicine* 34: 2090-2098.

- Suarez-Sipmann F and Bohm S. (2009) Recruit the lung before titrating the right positive end-expiratory pressure to protect it. *Critical Care* 13: 134.
- Suarez-Sipmann F, Bohm SH, Tusman G, et al. (2007) Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. *Crit Care Med* 35: 214 - 221.
- Suki B, Alencar AM, Sujeer MK, et al. (1998) Life-support system benefits from noise. *Nature* 393: 127-128.
- Sundaresan A, Chase J, Shaw G, et al. (2011a) Model-based optimal PEEP in mechanically ventilated ARDS patients in the Intensive Care Unit. *BioMedical Engineering OnLine* 10: 64.
- Sundaresan A and Chase JG. (2011) Positive end expiratory pressure in patients with acute respiratory distress syndrome - The past, present and future. *Biomedical Signal Processing and Control* 7: 93-103.
- Sundaresan A, Geoffrey Chase J, Hann CE, et al. (2011b) Dynamic functional residual capacity can be estimated using a stress-strain approach. *Computer Methods and Programs in Biomedicine* 101: 135-143.
- Sundaresan A, Yuta T, Hann CE, et al. (2009) A minimal model of lung mechanics and model-based markers for optimizing ventilator treatment in ARDS patients. *Computer Methods and Programs in Biomedicine* 95: 166-180.
- Suter P, Fairley B and Isenberg M. (1975) Optimum End-Expiratory Airway Pressure in Patients with Acute Pulmonary Failure. *N Engl J Med* 292: 284-289.
- Suter PM, Fairley HB and Isenberg MD. (1978) Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. *Chest* 73: 158 - 162.
- Sydow M, Burchardi H, Ephraim E, et al. (1994) Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. *Am J Respir Crit Care Med* 149: 1550 - 1556.
- Szlavec A, Chiew Y, Redmond D, et al. (2014) The Clinical Utilisation of Respiratory Elastance Software (CURE Soft): a bedside software for real-time respiratory mechanics monitoring and mechanical ventilation management. *BioMedical Engineering OnLine* 13: 140.
- Talmor D, Sarge T, Malhotra A, et al. (2008) Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury. *New England Journal of Medicine* 359: 2095-2104.
- Talmor D, Sarge T, O'Donnell CR, et al. (2006) Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med* 34: 1389 - 1394.
- Thammanomai A, Hamakawa H, Bartolák-Suki E, et al. (2013) Combined Effects of Ventilation Mode and Positive End-Expiratory Pressure on Mechanics, Gas Exchange and the Epithelium in Mice with Acute Lung Injury. *PLoS ONE* 8: e53934.
- The Acute Respiratory Distress Syndrome Network. (2000) Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med* 342: 1301-1308.
- The ARDS Definition Task Force A. (2012) Acute respiratory distress syndrome: The berlin definition. *JAMA: The Journal of the American Medical Association* 307: 2526-2533.
- The ARDS Network. (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342: 1301 - 1308.
- The ARDS Network. (2003) Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Critical Care Medicine* 31: 2592-2597.

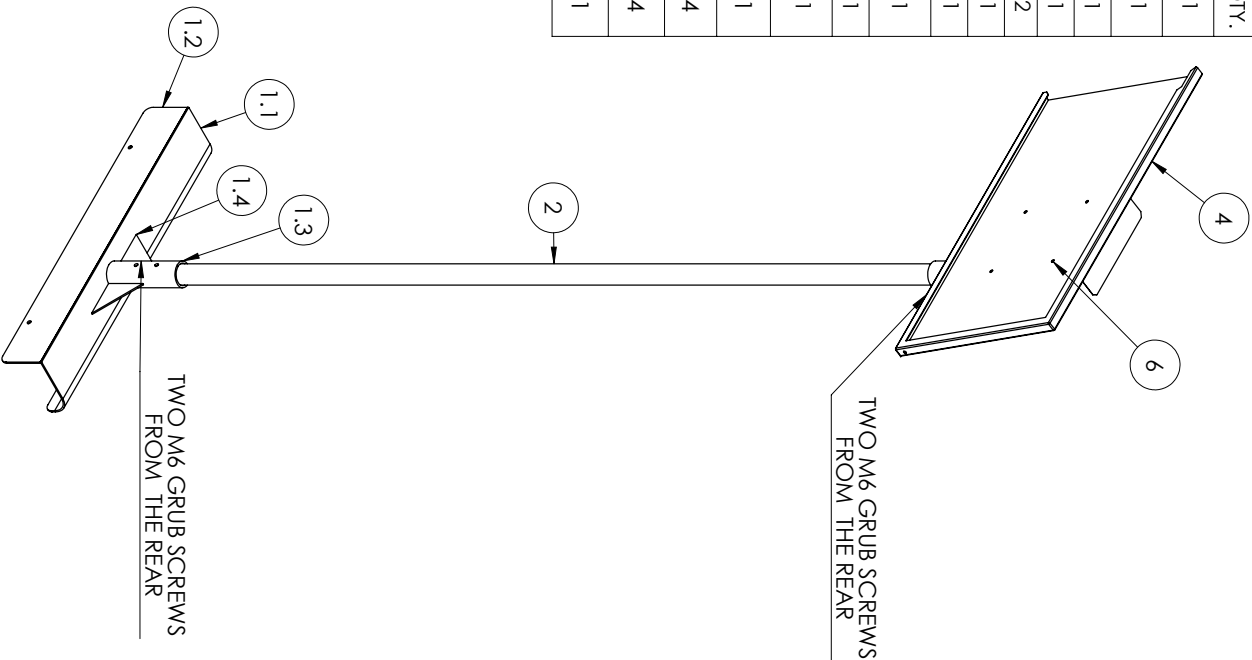
- The ART Investigators. (2012) Rationale, study design, and analysis plan of the Alveolar Recruitment for ARDS Trial (ART): Study protocol for a randomized controlled trial. *Trials* 13.
- Thomsen L, Karbing D, Smith B, et al. (2013) Clinical refinement of the automatic lung parameter estimator (ALPE). *Journal of Clinical Monitoring and Computing* 27: 341-350.
- Toung TJK, Saharia P, Mitzner WA, et al. (1978) The beneficial and harmful effects of positive end expiratory pressure. *Surgery Gynecology and Obstetrics* 147: 518-524.
- Treggiari MM, Romand JA, Martin JB, et al. (2002) Air cysts and bronchiectasis prevail in nondependent areas in severe acute respiratory distress syndrome: a computed tomographic study of ventilator-associated changes. *Crit Care Med* 30: 1747 - 1752.
- van Drunen E, Chiew YS, Chase J, et al. (2013) Expiratory model-based method to monitor ARDS disease state. *BioMedical Engineering OnLine* 12: 57.
- Venegas JG, Harris RS and Simon BA. (1998) A comprehensive equation for the pulmonary pressure-volume curve. *J Appl Physiol* 84: 389 - 395.
- Villar J. (2005) Ventilator or physician-induced lung injury? *Minerva Anesthesiol* 71: 255 - 258.
- Villar J, Kacmarek R, Perez-Mendez L, et al. (2006) A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. *Crit Care Med* 34: 1311 - 1318.
- Villar J and Kacmarek RM. (2012) The American-European Consensus Conference definition of the acute respiratory distress syndrome is dead, long live positive end-expiratory pressure! *Medicina Intensiva* 36: 571-575.
- Villar J, Pérez-Méndez L, López J, et al. (2007) An Early PEEP/FiO₂ Trial Identifies Different Degrees of Lung Injury in Patients with Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine* 176: 795-804.
- Walker G. (2012) A review of technologies for sensing contact location on the surface of a display. *Journal of the Society for Information Display* 20: 413-440.
- Ware LB and Matthay MA. (2000) The Acute Respiratory Distress Syndrome. *N Engl J Med* 342: 1334-1349.
- Weg JG, Anzueto A, Balk RA, et al. (1998) The Relation of Pneumothorax and Other Air Leaks to Mortality in the Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 338: 341-346.
- Wunder C, Eichelbrönnner O and Roewer N. (2004) Are IL-6, IL-10 and PCT plasma concentrations reliable for outcome prediction in severe sepsis? A comparison with APACHE III and SAPS II. *Inflammation Research* 53: 158-163.
- Zambon M and Vincent J-L. (2008) Mortality Rates for Patients With Acute Lung Injury/ARDS Have Decreased Over Time*. *Chest* 133: 1120-1127.
- Zhao Z, Steinmann D, Frerichs I, et al. (2010) PEEP titration guided by ventilation homogeneity: a feasibility study using electrical impedance tomography. *Crit Care* 14: R8.
- Zilberberg Marya D and Epstein Scott K. (1998) Acute Lung Injury in the Medical ICU . Comorbid Conditions, Age, Etiology, and Hospital Outcome. *Am J Respir Crit Care Med* 157: 1159-1164.

Appendix A: Full Engineering Drawings

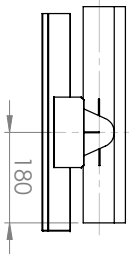


UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS				FINISH		DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
TOLERANCES:				SURFACE FINISH:		RADIOUS:		ANGULAR:		TITLE:	
NAME	SIGNATURE	DATE								CURe Soft Hardware Installation - Christchurch Hospital ICU	
DRAWN	V. MOIR	9 Mar 15									
CHECKED	Y. CHEN	13 Mar 15									
APPROVED											
MEG											
QA										DWG NO.	A3
				MATERIAL:		WEIGHT:		SCALE: 1:20		SHEET 1 OF 9	

ITEM NO.	PART NUMBER	QTY.
1	Chassis Mount Assembly	1
1.1	Chassis Mount Top and Back Folded	1
1.2	Chassis Mount Front	1
1.3	Boss	1
1.4	Boss Triangular Rib	2
2	Upright Support	1
3	VESA Mount Assembly	1
3.1	VESA Mount Plate Bent	1
3.2	Boss	1
3.3	VESA Mount Triangular Rib	1
4	1502i Sleeve	1
5	M6 x 8mm Grub Screws	4
6	Ø 4x 10mm Blind Rivets	4
7	IPX1 Cover Folded	1

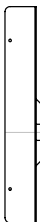


ISOMETRIC VIEW
SCALE 1:6

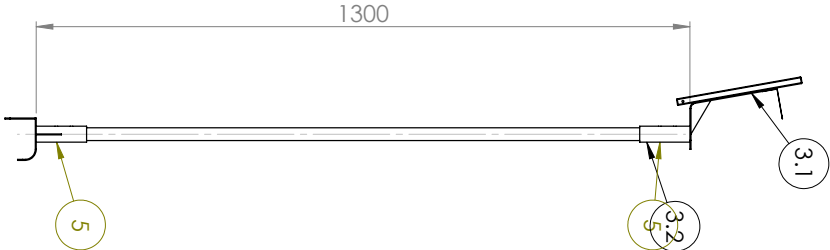


PLAN VIEW
SCALE 1:10

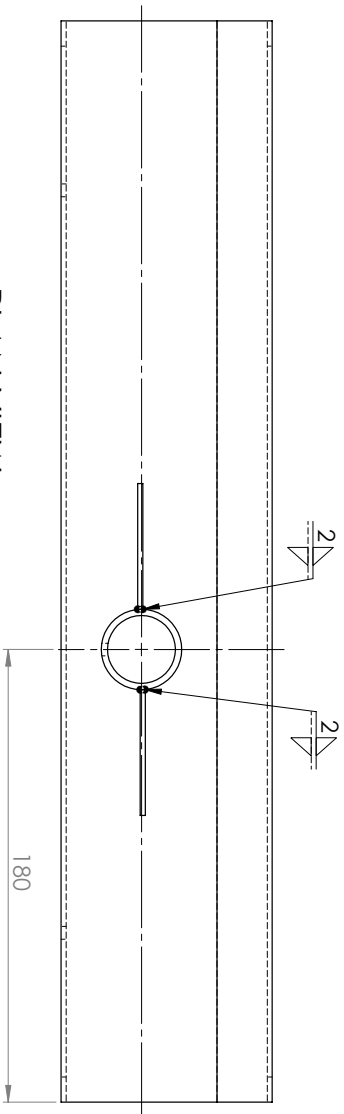
FRONT ELEVATION
SCALE 1:10



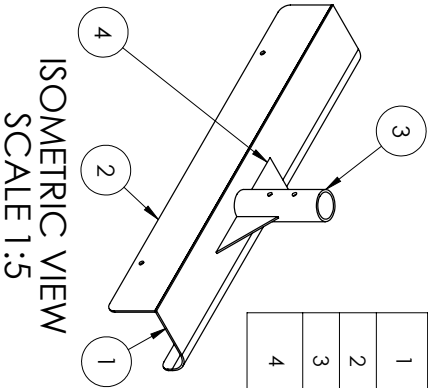
SIDE ELEVATION
SCALE 1:10



UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS				FINISH		DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
TOLERANCES:				SURFACE FINISH:		TOLERANCES:		TITLE:		CURE Soft Hardware Installation - Christchurch Hospital ICU	
ANGULAR:				NAME		SIGNATURE		DATE		DRAWN	
				V. Major				9 Apr 15		CHKD	
				Y. Chew				13 Apr 15		APPRD	
				MFG						MATERIAL:	
				G.A.						Stainless Steel 304	
										DWG NO.	
										Subassembly 1	
										A3	

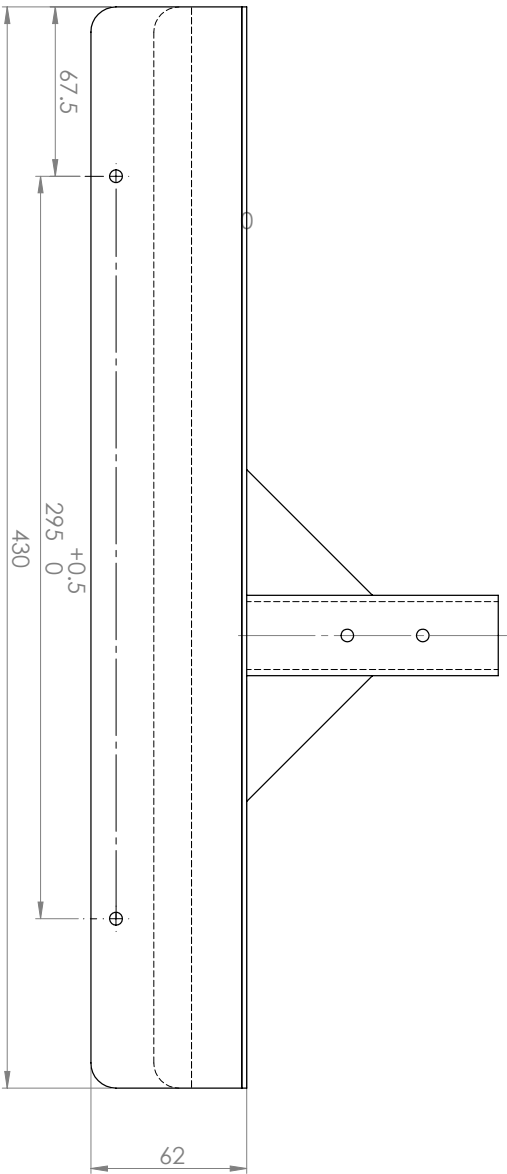


PLAN VIEW
SCALE 1:2

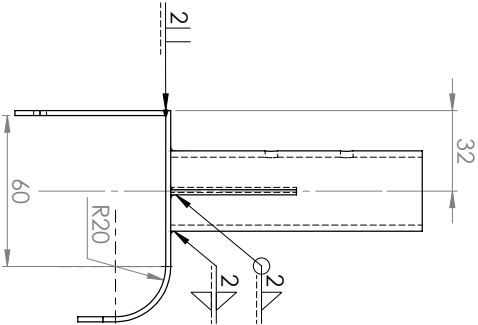


ISOMETRIC VIEW
SCALE 1:5

ITEM NO.	PART NUMBER	QTY.
1	Chassis Mount Top and Back Folded	1
2	Chassis Mount Front	1
3	Boss	1
4	Boss Triangular Rib	2



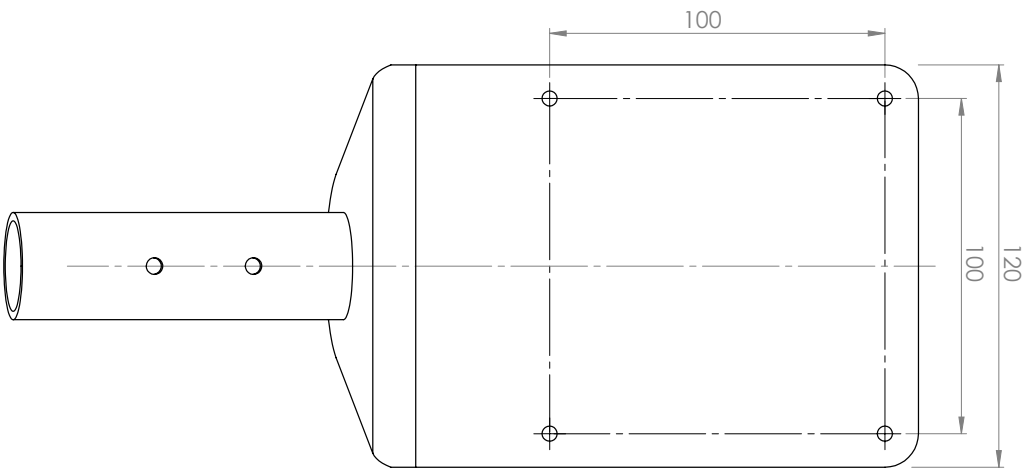
FRONT ELEVATION
SCALE 1:2



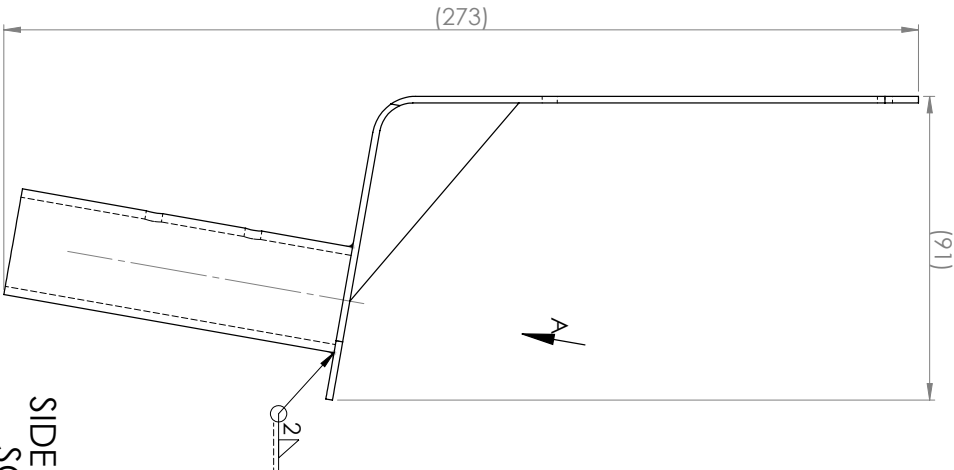
SIDE ELEVATION
SCALE 1:2

VENTILATOR
CHASSIS
MOUNTING
BRACKET

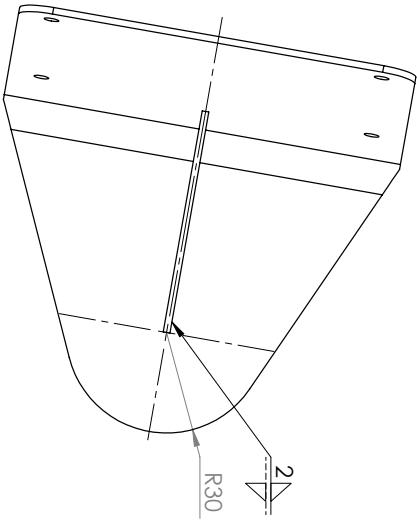
UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS			FINISH: No. 1 Hot rolled, annealed and pickled		DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
TOLERANCES: LINEAR: ANGULAR:										
NAME	SIGNATURE	DATE								
DRAWN	V. Major	9 Mar 15								
CHECKED	Y. Chew	13 Mar 15								
APPROVED										
MEG										
QA										
MATERIAL: Stainless Steel 304			DWG NO.		CURE Soft Hardware Installation - Christchurch Hospital ICU				A3	
WEIGHT:			SCALE: 1:5		SHEET 3 OF 9					



FRONT ELEVATION
SCALE 2:3



SIDE ELEVATION
SCALE 2:3



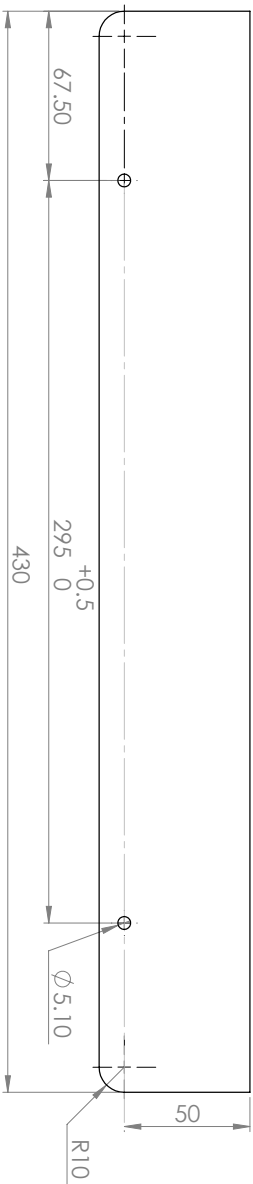
VIEW A
SCALE 2 : 3

ITEM NO.	PART NUMBER	QTY.
1	VESA Mount Bent	1
2	Boss	1
3	VESA Mount Rib	1

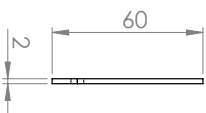
UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS				FINISH: No. 1 Hot rolled, annealed and pickled		DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
TOLERANCES: DIMENSIONS ANGULAR:											
DRAWN	NAME	SIGNATURE	DATE								
CHECKED	V. MOJO		9 Apr 15								
APPROVED	Y. CHIEW		13 Mar 15								
MEG											
G.A.											
				MATERIAL:				DWG NO.			
				Stainless Steel 304				Manufacturing 2			
				WEIGHT:				SCALE: 1:5		SHEET 4 OF 9	
										A3	

BENT
VESA
MOUNT

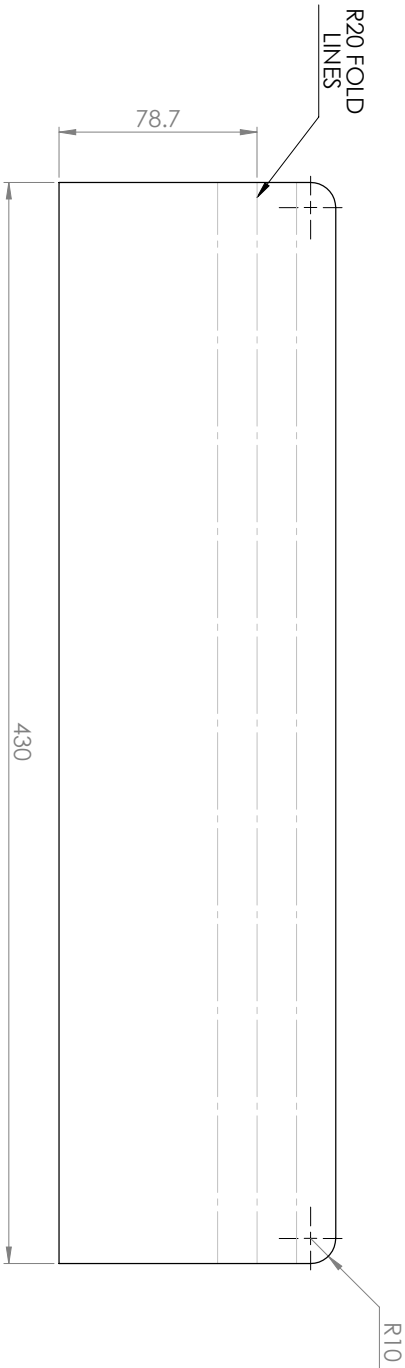
CURE Soft Hardware Installation
- Christchurch Hospital ICU



FRONT ELEVATION
SCALE 1:2

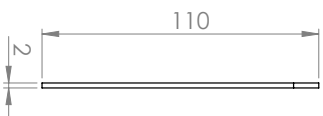


SIDE ELEVATION
SCALE 1:2

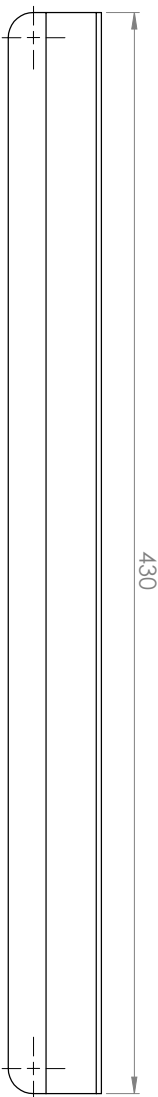


AFTER FOLDING

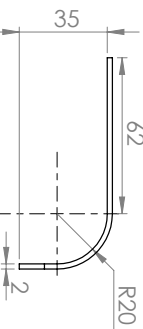
FRONT ELEVATION
SCALE 1:2



SIDE ELEVATION
SCALE 1:2



FRONT ELEVATION
SCALE 1:2



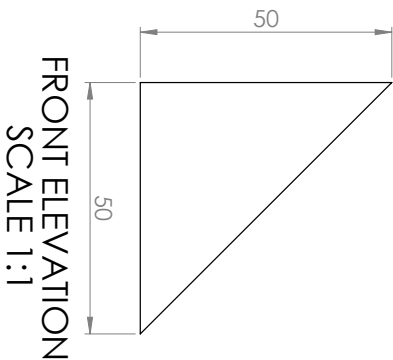
SIDE ELEVATION
SCALE 1:2

CHASSIS
MOUNT
TOP &
BACK
FOLDED

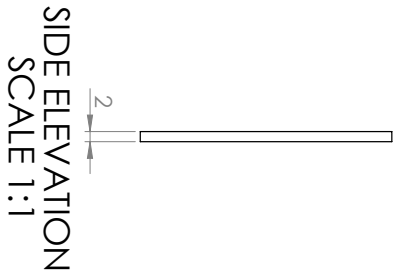
CHASSIS
MOUNT
FRONT
PLATE

CHASSIS MOUNT PARTS

UNLESS OTHERWISE SPECIFIED: DIMENSIONS ARE IN MILLIMETERS				FINISH: No. 1 Hot rolled, annealed and pickled		DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
TOLERANCES: ANGULAR:											
DRAWN	NAME	SIGNATURE	DATE								
	V MAJOR		9 Mar 15								
CHECKED	Y CHIEW		13 Mar 15								
APPROVED											
MFG											
G.A.											
				MATERIAL: Stainless Steel 304				DWG NO. Manufacturing 3			
				WEIGHT:				SCALE: 1:2			
								SHEET 5 OF 9			

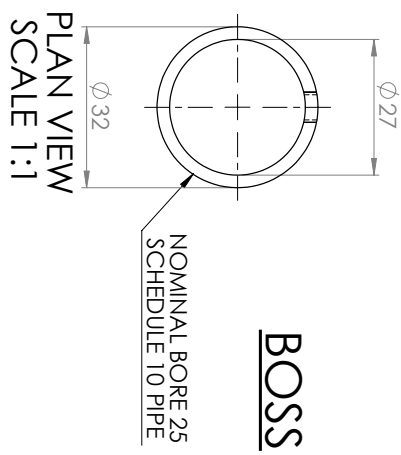


FRONT ELEVATION
SCALE 1:1



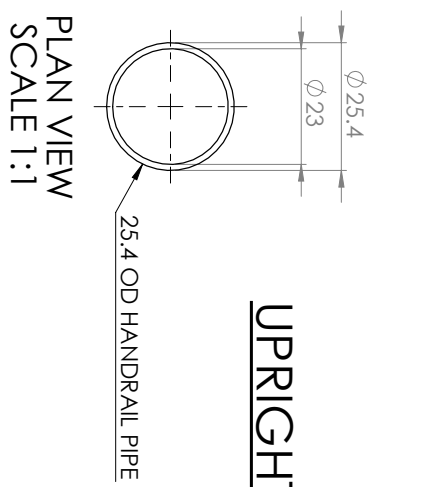
SIDE ELEVATION
SCALE 1:1

BOSS
TRIANGULAR
RIB



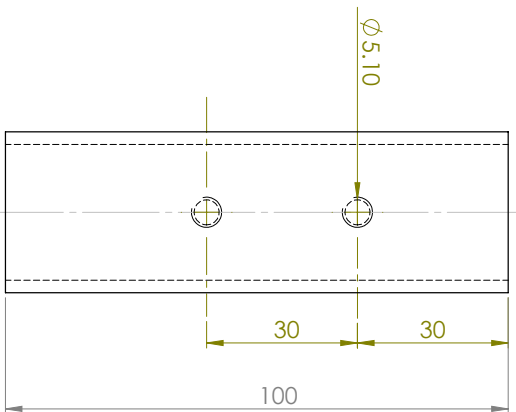
PLAN VIEW
SCALE 1:1

BOSS



PLAN VIEW
SCALE 1:1

UPRIGHT SUPPORT



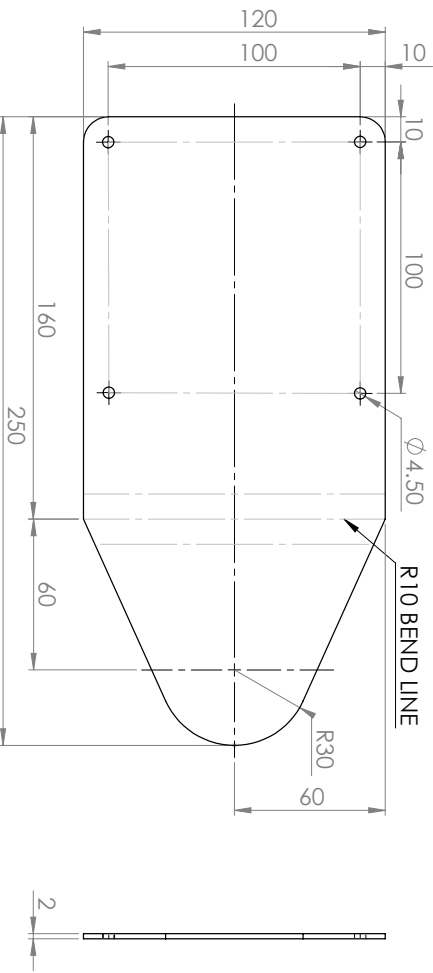
FRONT ELEVATION
SCALE 1:1



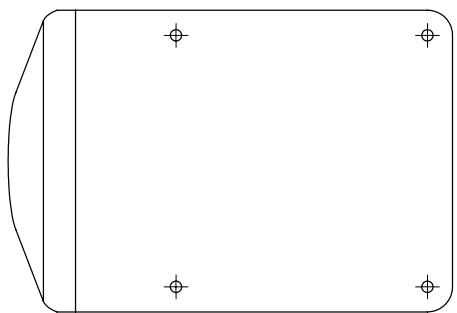
FRONT ELEVATION
SCALE 1:10

CHASSIS
MOUNT AND
UPRIGHT
SUPPORT
PARTS

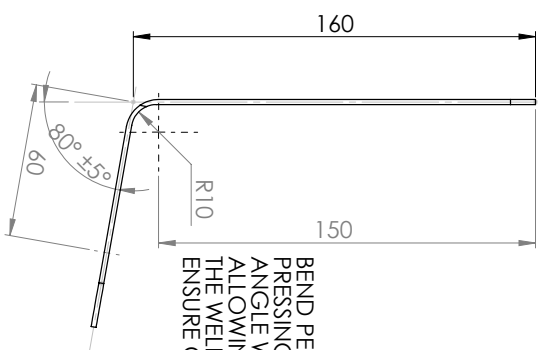
UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS				FINISH: No. 1		DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
SURFACE FINISH: TOLERANCES: ANGULAR:				Hot rolled, annealed and pickled							
NAME		SIGNATURE		DATE				TITLE:			
DRAWN: V Major				9 Mar 15				CURE Soft Hardware Installation - Christchurch Hospital ICU			
CHECKED: Y Chew				13 Mar 15							
APPROVED:											
MEG											
G.A.						MATERIAL:		Manufacturing 4			
						Stainless Steel 304					
						WEIGHT:		SCALE: 2:1		SHEET 6 OF 9	
										A3	



VESA MOUNT PLATE TO FOLD

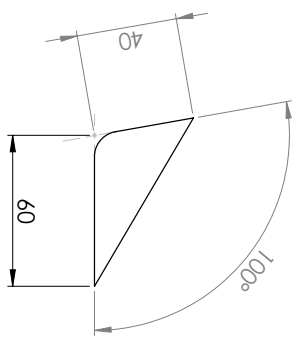


FRONT ELEVATION
SCALE 1:2

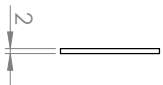


SIDE ELEVATION
SCALE 1:2

BEND PERFORMED BY
PRESSING INTO V OF EQUAL
ANGLE WITH A Ø 10 BAR AND
ALLOWING SPRINGBACK.
THE WELDING PROCESS WILL
ENSURE CORRECT ANGLE.



FRONT ELEVATION
SCALE 1:2



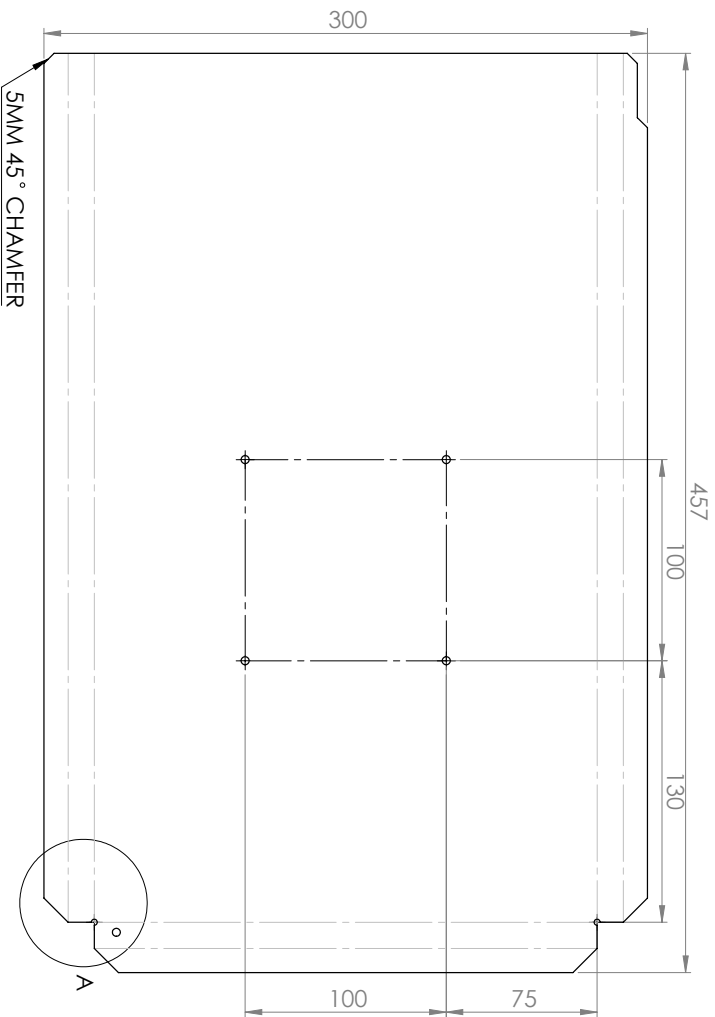
SIDE ELEVATION
SCALE 1:2

VESA MOUNT TRIANGULAR RIB

VESA MOUNT PARTS

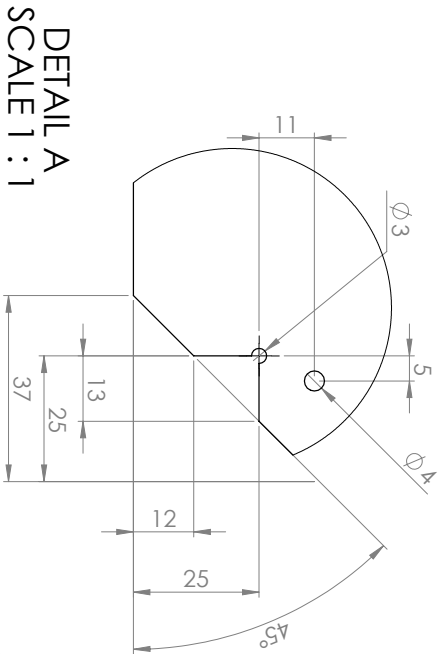
UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS				FINISH		DETAIL AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
TOLERANCES:				No. 1 Hot rolled, annealed and pickled							
ANGULAR:											
NAME	SIGNATURE	DATE									
DRAWN	V. Major	9 Mar 15									
CHECKED	V. Chew	13 Mar 15									
APPROVED											
MFG											
G.A.											
				MATERIAL:				DWG NO.			
				Stainless Steel 304				Manufacturing 5			
				WEIGHT:				SCALE: 1:2		SHEET 7 OF 9	
										A3	

CURE Soft Hardware Installation
- Christchurch Hospital ICU



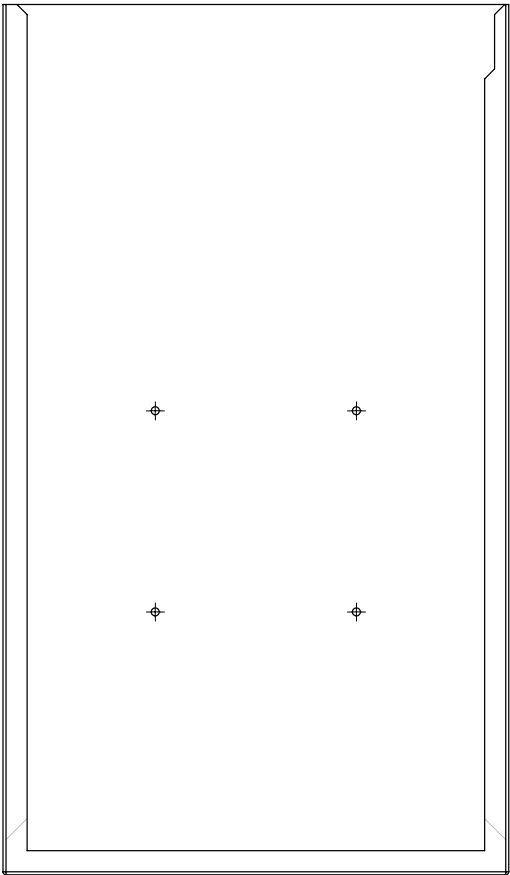
FRONT ELEVATION
SCALE 2:5

1502i SLEEVE
UNFOLDED



DETAIL A
SCALE 1 : 1

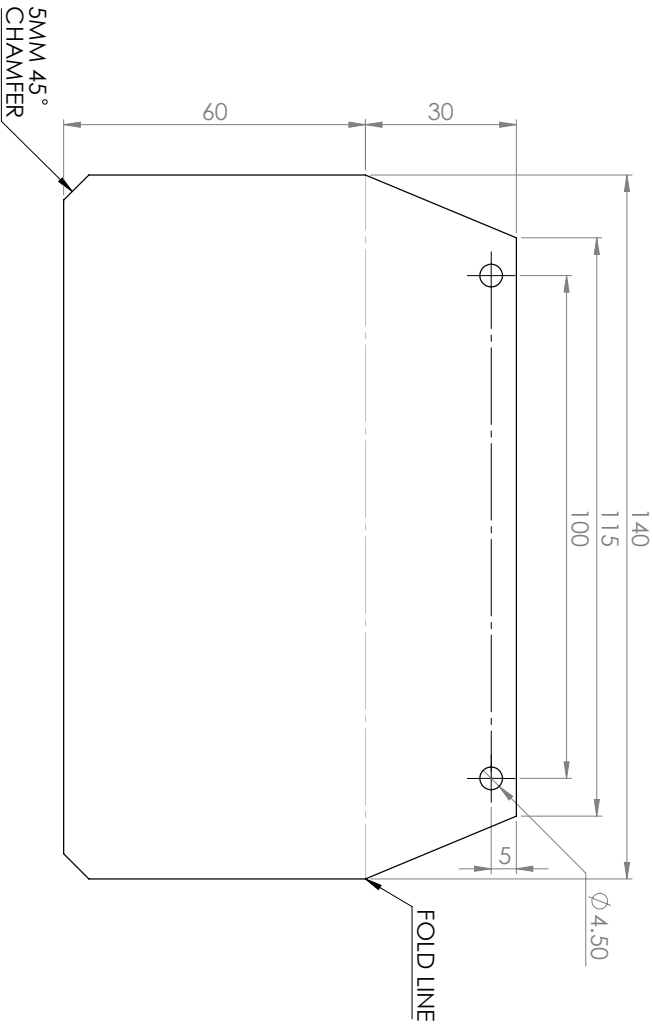
STAINLESS
1502i SLEEVE



FRONT ELEVATION
SCALE 2:5

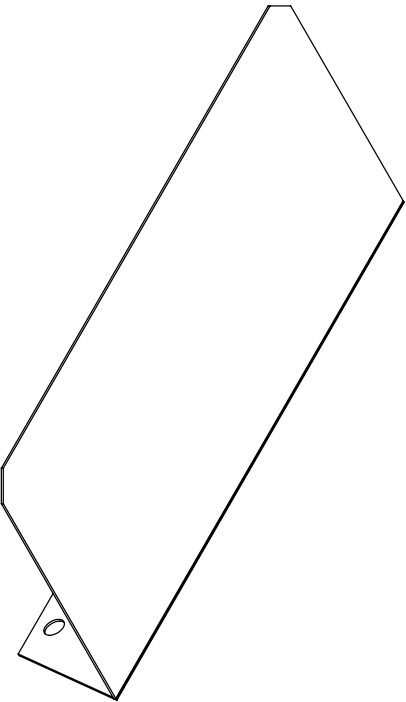
1502i SLEEVE
FOLDED

UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS				FINISH		DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION	
TOLERANCES:				SURFACE FINISH:		TOLERANCES:		TOLERANCES:		TOLERANCES:	
ANGULAR:				ANGULAR:		ANGULAR:		ANGULAR:		ANGULAR:	
NAME	SIGNATURE	DATE									
DRAWN	V. MOJO	20 Mar 15									
CHECKED											
APPROVED											
MFG											
G.A.											
				MATERIAL:		0.5MM 304 SS SHEET		DWG NO.		Manufacturing 6	
				TITLE:		CURE Soft Hardware Installation - Christchurch Hospital ICU		SHEET 8 OF 9		A3	



FRONT ELEVATION
SCALE 1:1

IPX1 COVER
UNFOLDED



ISOMETRIC VIEW
SCALE 1:1

IPX1 COVER
FOLDED

STAINLESS
IPX1 COVER

UNLESS OTHERWISE SPECIFIED, DIMENSIONS ARE IN MILLIMETERS				FINISH	DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING		REVISION
SURFACE FINISH:									
TOLERANCES:									
ANGULAR:									
DRAWN	NAME	SIGNATURE	DATE				TITLE:		
CHKD	V.MOJO		20 Mar 15				CURE Soft Hardware Installation - Christchurch Hospital ICU		
APPVD									
MEG									
QA									
							MATERIAL:		
							0.5MM 304 SS SHEET		
							DWG NO.		
							Manufacturing 7		
							SCALE: 1:2		
							SHEET 9 OF 9		
							A3		

CUREsoft Training Manual

For doctors, nurses and researchers



Patient Eligibility and Grouping

All invasively ventilated patients who come into ICU will be screened with inclusion and exclusion criteria as to whether they are eligible to be included in the trial.

First, a paper-based checklist will compare the patient against the inclusion/exclusion criteria. Second, patient information is entered into the randomisation software and each eligible patient is randomised into either **SPV (standards practice ventilation)** or **MBV (model-based ventilation)**. Both groups are participants in the CUREsoft trial.

It is very important that data from every participant gets collected.

Setting Up the Hardware and Ventilator

- Each unit consists of a computer and touchscreen monitor mounted on a metal stand that is secured on the back of the ventilator. The unit is secured with two finger screws at the base of the ventilator and an elastic tie around the ventilator frame.
- When not in use, the stands will be stored in the technician area with the other equipment.
- Two connections need to be made to the ventilator:
 1. The power cable needs to be connected to the three-pin plug on the right hand side of the ventilator.
 2. The 9-pin plug must be connected to **socket 3** on the rear of the ventilator monitor. To ensure data can flow, under the Communication Setup tab on the ventilator, the options must be set to **Waveforms** with a Baud Rate of **38400**.
- Once the computer power is connected the computer can be turned on by pressing the single button on the rear black coloured panel. The button should illuminate blue.

Logging on to the Computer

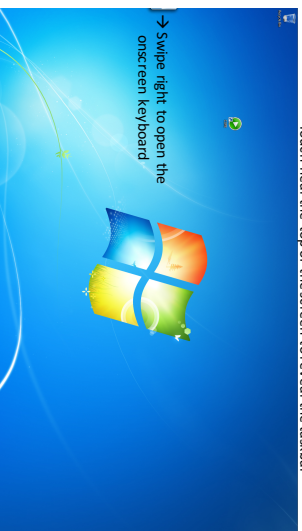
Each computer has two log-ins

1. Admin – used only for software development, and
2. CURE01, 02 etc. – this is the primary log-in for the CUREtrial and will be the only log-in you use.

No password is required to log-in to CURE01 or 02 etc.

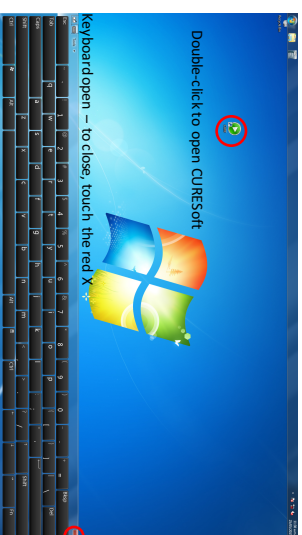
Computer layout

Touch near the top of the screen to reveal the taskbar



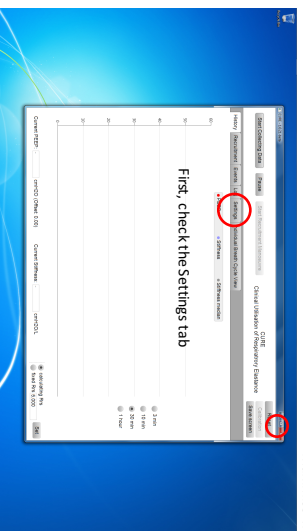
Computer layout

Taskbar and start menu as normal

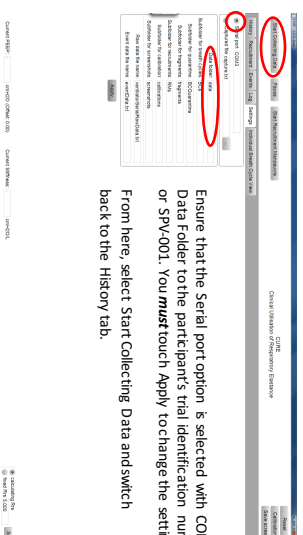


Opening CUREsoft

Maximise with the usual button



Settings Tab



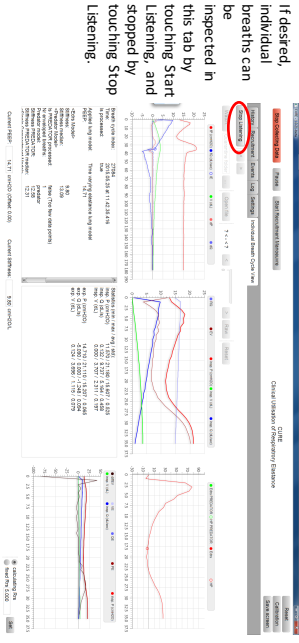
Ensure that the Serial port option is selected with COM3 and change the Data Folder to the participant's trial identification number i.e. MBV-001 or SPV-001. You *must* touch Apply to change the settings.
From here, select Start Collecting Data and switch back to the History tab.

History Tab



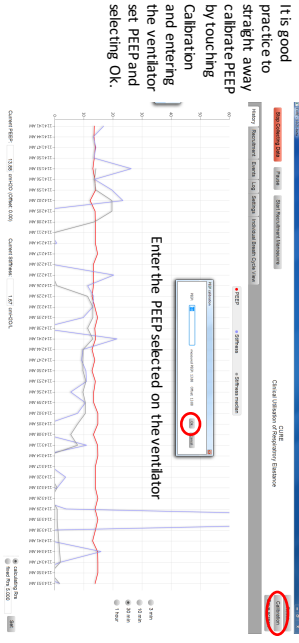
The Start Collecting Data button will turn red. Data will start to be collected and plotted in this tab.

Individual Breath Cycle View Tab



If desired, individual breaths can be inspected in this tab by touching Start Listening, and stopped by touching Stop Listening.

PEEP Calibration



It's good practice to straight away calibrate PEEP by touching Calibration and entering the ventilator set PEEP and selecting Ok.

Maximum Recruitment Manoeuvre

For participants in the Intervention MBV group *only*

A maximum recruitment manoeuvre (MaxRM) procedure is only completed once per patient at the start of ventilation unless a doctor decides to repeat.

Prior to MaxRM:

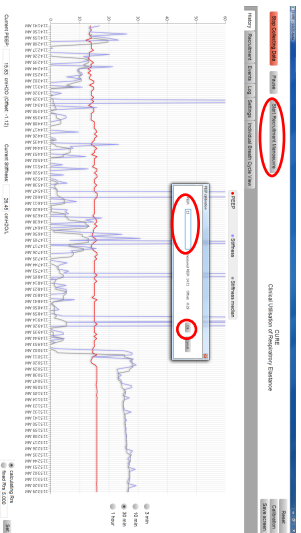
- Increase the patient airway cuff pressure to 50 cmH₂O
- Administer appropriate muscle relaxant and sedation
- Set peak airway pressure alarm on ventilator to 55 cmH₂O

For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

Once CURE easance has stabilised, a recruitment manoeuvre must be run.

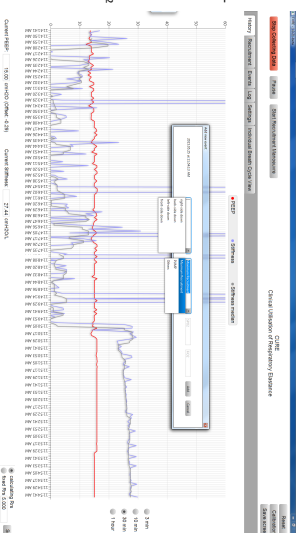
Touch Start Recruitment Manoeuvre, enter the ventilator selected PEEP and touch Ok.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

Enter the patient position (usually back-side down), the protocol to follow maxIMV or PUMP, the SP_{O_2} and FI_{O_2} and touch Add.

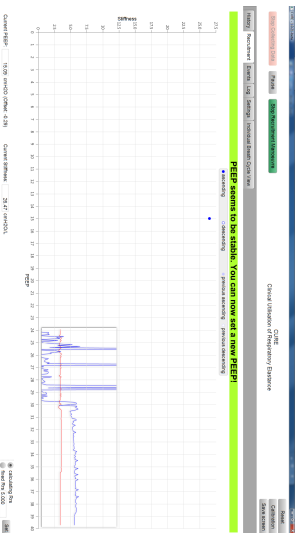


For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

Starting the RM will move the interface to this, the Recruitment tab.

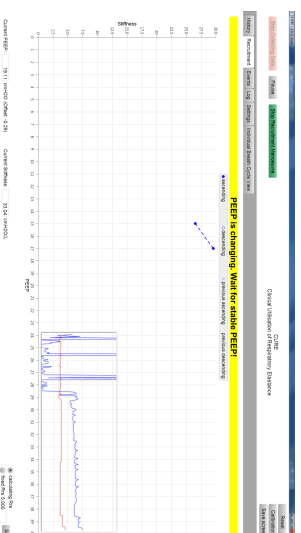
The window in the bottom right corner is the history figure.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

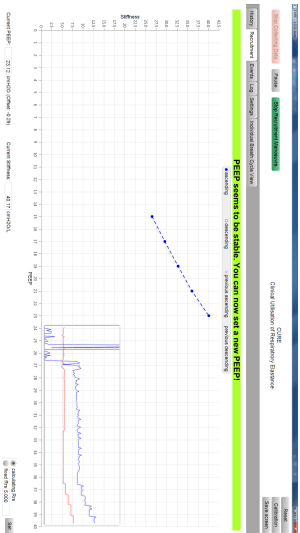
The yellow banner informs you that PEEP is changing and you must wait.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

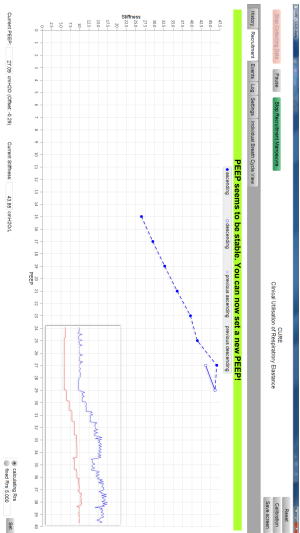
The green banner informs you that PEEP has stabilised and PEEP can be adjusted.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

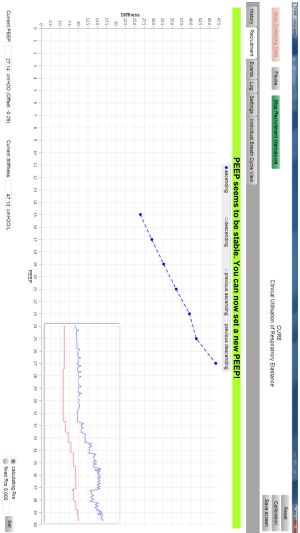
Once the max PEEP has been reached and PEEP is decreased, the points and lines will appear differently.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

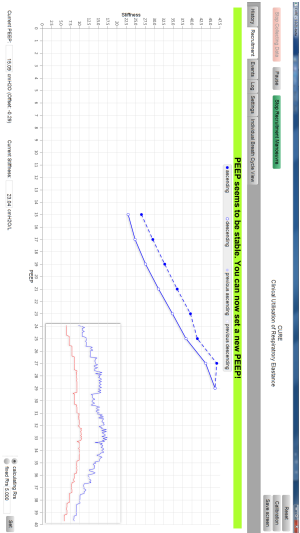
For each PEEP increment, the software will plot one point, the stiffness at the matching PEEP. As PEEP is changed the points are connected.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

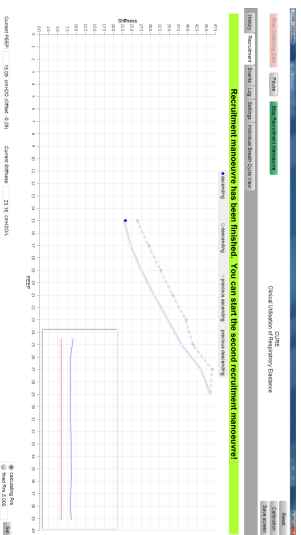
At the same PEEP you started at a PUMP will be complete whereas a maxRM needs to increase and decrease again.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

The software detects this point and reminds you to continue for a maxRM.



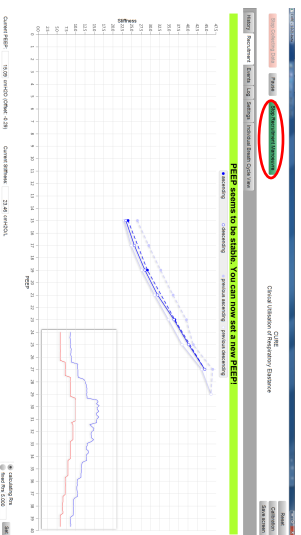
For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

Back down and the maxRM is complete!

Once done, touch Stop Recruitment Manoeuvre.

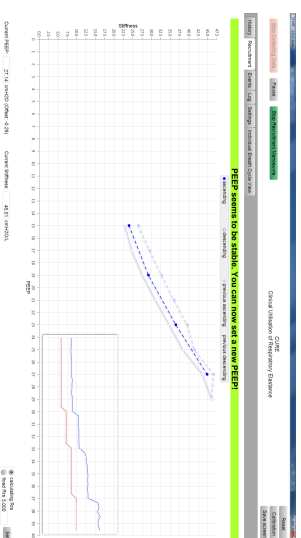
Return the cuff pressure back to -30 cmH₂O and reset ventilator alarms.



For participants in the intervention MBV group [only](#)

Maximum Recruitment Manoeuvre

Going up again!

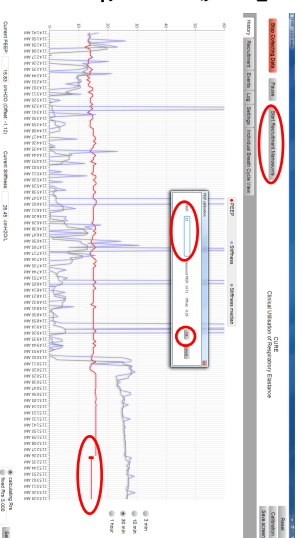


For participants in the intervention MBV group [only](#)

PUMP Protocol

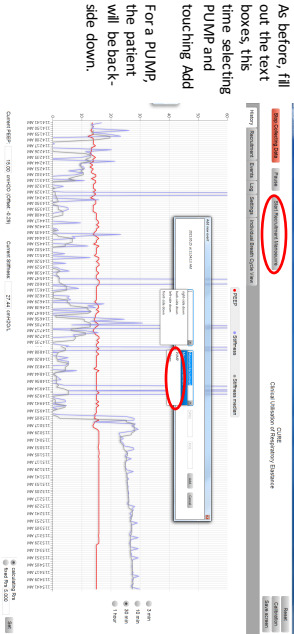
A PUMP is a snail maxRM to be performed each time the patient is turned onto their back.

Firstly, reduce PEEP by 2 cmH₂O and touch Start Recruitment Manoeuvre and calibrate PEEP.



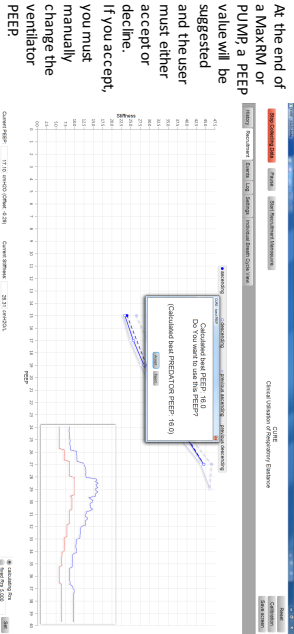
PUMP Protocol

For participants in the intervention MBV group only



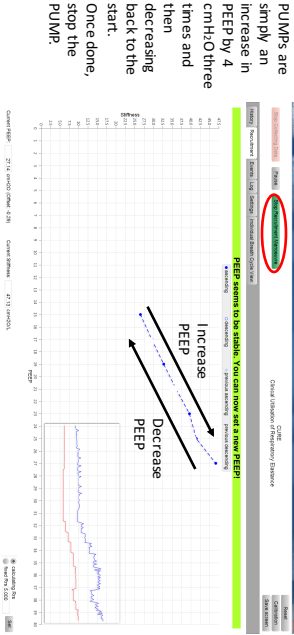
PEEP Suggestion

For participants in the intervention MBV group only



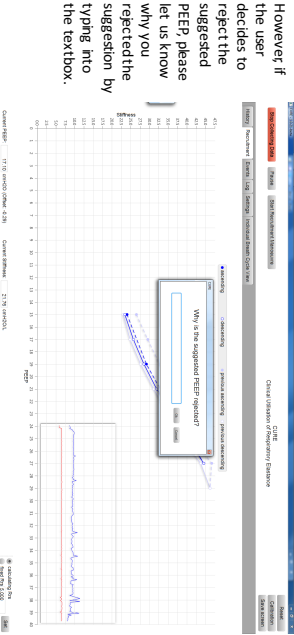
PUMP Protocol

For participants in the intervention MBV group only



PEEP Suggestion

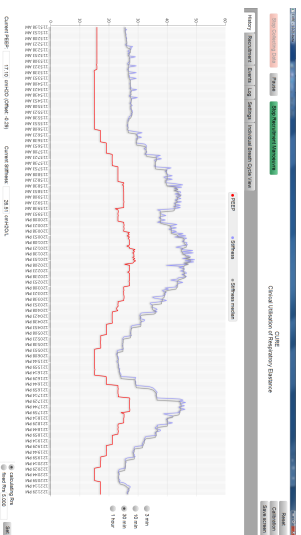
For participants in the intervention MBV group only



For participants in the intervention MBV group [only](#)

Back to the History Tab

A maxRM looks similar to this in the History tab and can take 20 minutes to perform.



Events Tab

Similar to the first step in a RM, users can state events in the Events tab. Examples are: turning the patient, desaturation events, coughing etc.



Libre Open Office

Also on the computers is a copy of Open Office. Please leave detailed notes here if you wish. Save the file to Documents.



Are There Any Questions?

Thank you very much.

Vincent Major, KT Kim
027 286 0069, 027 300 5899

Appendix C: Screening Sheet

PATIENT IS ON INVASIVE MECHANICAL VENTILATION (MV)

Inclusion criteria:

Patient:

1.	Diagnosed with ARDS by intensive care clinicians as per Berlin Definition*
2.	Arterial line in situ

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging ^a	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation ^b	
Mild	200 mm Hg < PaO ₂ /FIO ₂ ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H ₂ O ^c
Moderate	100 mm Hg < PaO ₂ /FIO ₂ ≤ 200 mm Hg with PEEP ≥5 cm H ₂ O
Severe	PaO ₂ /FIO ₂ ≤ 100 mm Hg with PEEP ≥5 cm H ₂ O

***“Berlin Definition of Acute Respiratory Distress Syndrome”**

The ARDS Definition Task Force, A. 2012

Abbreviations: CPAP, continuous positive airway pressure; FIO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

^aChest radiograph or computed tomography scan.

^bIf altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO₂/FIO₂ × (barometric pressure/760)].

^cThis may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Exclusion criteria:

Patient:

1.	Likely to be discontinued from MV within 24 hours
2.	< 16 years old
3.	Moderate or severe traumatic brain injury, and/or a measured ICP ≥ 20cmH₂O
4.	Any medical condition associated with a clinical suspicion of raised ICP
5.	High spinal cord injury with loss of motor function
6.	Significant weakness from any neurological disease
7.	Barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema or any intercostal catheter for the treatment of air leak)
8.	Asthma as primary presenting condition or a history of significant COPD
9.	Moribund and/or not expected to survive for >72 hours
10.	Have received MV for > 48 hours (including time spent ventilated in a referring unit)
11.	Lack of clinical equipoise by intensive care unit (ICU) medical staff managing the patient
12.	Readmitted to ICU within 28 days of the first day entered into the study
13.	Readmitted to ICU at any time if they have participated in the study during the same hospital admission

Abbreviations:

ICP: Intracranial Pressure

COPD: Chronic Obstructive Pulmonary Disease

Paste the Patient info here

Patient Info:

Ethnicity : _____

ICU Admission Date : _____

Clinical Diagnostic: _____

Is the patients under Apache III diagnostic code 200 or 1300: Yes No

PaO₂: _____ FiO₂: _____ SPO₂: _____

Inclusion Criteria (Tick if applicable)

	1. Patients requiring invasive mechanical ventilation (MV) (intubation or tracheotomy)
	2. Patients diagnosed with acute respiratory distress syndrome (ARDS) of any severity (PF [Oxygen partial pressure to fraction of inspired oxygen] ratio <300mmHg) by intensive care clinicians.
	3. Arterial line in situ.

Exclusion Criteria (Tick if applicable)

	1. Patient who are likely to be discontinued from MV within 24 hours.
	2. Patient with age < 16.
	3. Patients who have moderate or severe traumatic brain injury, and/or a measured intracranial pressure \geq 20 cmH ₂ O
	4. Patients who have a high spinal cord injury with loss of motor function and/ or have significant weakness from any neurological disease.
	5. Patients who have a Barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema or any intercostal catheter for the treatment of air leak).
	6. Patients who have asthma as the primary presenting condition or a history of significant chronic obstructive pulmonary disease.
	7. Patients who are moribund and/or not expected to survive for > 72 hours.
	8. Patients who have already received MV for > 48 hours (including time spent ventilated in a referring unit).
	9. Lack of clinical equipoise by intensive care unit (ICU) medical staff managing the patient.

Is the Patient eligible for CURE RCT: Yes No

*If Yes, which RCT group is the patient assigned to: Control / Intervention

Fill this portion only after patients/ family/ relative/ Whanau has been contacted and informed about CURE

Is the Family/Relative/Whanau consenting to the trials: Yes No Date: _____

If Yes, complete consent forms.

If No, please remove the patient from trial and update Excel forms.

Is the Patient consenting to the trials: Yes No Date: _____

If Yes, complete consent forms.

If No, please remove the patient from trial and update Excel forms.

Updated by: _____

Date: _____

Information Sheet for Relative, Friend, Family/Whanau

Clinical Utilisation of Respiratory Elastance: the ‘CURE’ Study

-Optimising PEEP in people on mechanical ventilation

Co-ordinating Investigator	
Assoc Professor Geoffrey M Shaw Intensivist Department of Intensive Care Medicine Private Bag 4710. Christchurch Mail Centre 8140 Christchurch Hospital Phone: (03) 364 1077	
Co Investigators	
Dist. Prof. J. Geoffrey Chase Professor at University of Canterbury Department of Mechanical Engineering University of Canterbury Phone: (03) 364 2987 ext 7224	Dr. Yeong Shiong Chiew Post Doctoral Researcher Fellow Department of Mechanical Engineering University of Canterbury Phone: (03) 364 2987

Participation

Your relative or friend is being mechanically ventilated because their lungs are not working properly. They are invited to take part in a study called a Clinical Utilisation of Respiratory Elastance (CURE) randomised control trial (RCT). This study is trying to find out whether ICU doctors and nurses using a computerised method of adjusting the ventilator settings can improve the care of people in ICU.

Before you consider whether your relative or friend would want to take part in this study, it is important that you read and understand this information sheet. It describes the purpose, procedures, and benefits of the study and your right to withdraw at any time.

Introduction

Intensive care doctors and nurses use ventilators to support a person’s breathing in intensive care. Pneumonia, trauma, inflammation, or too much fluid in the lung stops it from working properly. When this happens the lung gets “stiff”; this makes breathing difficult. The lungs become stiffer because the injury or infection causes many of the air sacs, (alveoli) to collapse. This is known as Acute Respiratory Distress Syndrome (ARDS).

Some people with stiff lungs will need their breathing helped by a ventilator. However, the ventilator, keeping them alive, may make their lungs worse. High breathing volumes and/or pressures can damage stiff lungs. Unfortunately, the lung can’t be rested and immobilised like a broken bone, so it is very important we ensure the ventilator does not cause more lung injury.

The stiffness of the lung may be reduced by carefully inflating the collapsed regions using a “recruitment manoeuvre” (RM). During a RM the lung is gently inflated over a number of breaths by not allowing the lung to completely breathe out. ICU doctors and nurses do this by increasing the Positive End Expiratory Pressure (PEEP) setting on the ventilator.

Our research aims to find out if people on mechanical ventilation in intensive care are helped by keeping their lung stiffness as low as possible through use of RMs and optimal levels of PEEP. In this way, we hope to minimise the damage done to the lung by the ventilator.

Selection

Your relative or friend has been asked to consider participation in this study because they are ventilated and have been diagnosed with ARDS.

The Study

Your relative or friend is currently being ventilated using settings chosen by the ICU doctors. Currently, doctors have no standard way of selecting PEEP, so they use their best guess. Too much PEEP overstretches the lung, while too little PEEP causes collapse. Too much, or too little, PEEP makes the lung stiffer. Every person’s lung is different, and his or her lung condition may also change during their stay in ICU. Therefore, choosing the level of PEEP can be quite tricky, and might not always be right.

The lung’s stiffness, or elastance, is measured directly at the bedside using a laptop computer. To help doctors decide the best settings, the PEEP will be changed upwards and then downwards. For each of the changes, their responses will be recorded.

Your relative or friend may be allocated to either A) a standard ventilation treatment or B) a ventilation treatment using a computerised method, which selects PEEP according to how stiff their lungs are. A randomised trial means every person, who is eligible to take part in this study, has an equal chance of receiving either treatment. This means the results of this research are not influenced by the ICU doctors or nurses.

If your friend or relative is in group A) they will receive usual ventilation care by ICU doctors and nurses. A computer will record the information from the ventilator, but this will not influence their care.

If your friend or relative is in group B) **a computer will record the information from the ventilator and recommend the best PEEP setting on the ventilator.** The doctors will use the PEEP calculated by the computer setting if they think it will help your relative’s or friend’s care. Their lung “stiffness” will change over time, so we will also check the lung stiffness at regular intervals and each time they are turned in bed. The PEEP settings will be adjusted as necessary.

Risks

There is a small risk that the PEEP setting suggested by the computer might not be the most suitable for your relative or friend. This risk is minimised by asking the doctor if they agree with the PEEP level suggested by the computer. If the ICU doctor is not satisfied with the computer’s suggestion, they will choose another PEEP, which they consider more appropriate. The computer cannot adjust the PEEP itself; an ICU staff member must manually change this setting.

Possible Benefits

Your relative or friend may or may not experience any benefits by taking part in this study. However, there will be more frequent attention paid to their ventilation and changes to the ventilator will be made more frequently, which may result in a faster recovery.

If our method is found to help people receiving ventilation in ICU, this treatment could become more widely adopted and significantly change the experiences of people in ICUs all over the world.

Compensation

In the unlikely event of a physical injury as a result of your friends/relatives participation in this study, they will be eligible to apply for accident compensation (ACC) within its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this trial.

ACC cover is not automatic and their case will need to be assessed by ACC according to the provisions of the 2001 Injury Prevention Rehabilitation and Compensation Act. If the claim is accepted by ACC, they still might not get any compensation. This depends on a number of factors such as whether they are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If your relative or friend has ACC cover, generally this will affect their right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

Stopping participation in this study

If your friend/relative takes part in this study, you are always free to offer your opinions about their ongoing participation at any time, without having to give a reason. This will not affect their continuing health care.

Your friend's/relative's doctors may stop this study, or their participation in this study, at any time, for any reason, without seeking your opinions. If this happens, it might be because their condition has changed, or because of technical problems relating to the equipment.

Investigator Payment

The investigators are not paid for this study.

Confidentiality

If you agree to your relative or friend taking part in this study, the information obtained will be shared amongst investigators within the Department of Intensive Care, and the Centre for Bioengineering, University of Canterbury. However, no sensitive information will be collected, discussed or shared even amongst the research team. Only information that is directly relevant to this study will be used.

On any documents relating to the study, only a study code, or local ICU admission number, will identify them. Their National Health Information (NHI) number or any personal details that could identify them will not be used. They will not be personally identified in any reports on this study. Their medical information will be processed on a computer and held for up to 20 years. Study information will be kept secure. De-identified information may be shared amongst other researchers in this field. Results of this study will be presented at conferences and submitted for publication in medical and

bioengineering journals. By signing the accompanying form, you consider your friend or relative would agree to participate in this research, the record review, information storage, and data transfer described above.

Research Funding

This research is supported by the Health Research Council of New Zealand (HRC).

Contact Details

For more information about this study, please feel free to contact the people below. You are also welcome to discuss this study with any of the Intensive Care doctors. You may telephone the ICU staff at any time (day or night) if you have any important concerns.

Health and Disability Services Consumer Advocate:

If you, your relative, or friend have any queries or concerns regarding their rights as a participant in this study, they may wish to contact a Health and Disability Services Consumer Advocate:

Telephone (03) 377 7501 or 0800 377 766 outside Christchurch.

Maori Health Support:

Eru Waiti

Maori Health Services

Canterbury District Health Board

Telephone: (03) 364 0640 Ext 88797; Mobile: 027 382 6587

Email: Eru.Waiti@cdhb.health.nz

Intensive Care:

Assoc Prof Geoffrey M Shaw (Co-ordinating Investigator)

Department of Intensive Care

Christchurch Hospital

Private Bag 4710

Christchurch 8011

Email: Geoff.Shaw@cdhb.health.nz

Intensive Care Unit Reception:

Direct Dial: (03) 364 1077

This study has received ethical approval from the Southern Health and Disability Ethics Committee.

Thank you for considering your relative or friend's participation in this study.



Geoff Shaw,

Co-ordinating Investigator

STATEMENT BY RELATIVE/FRIEND/FAMILY/WHANAU
Clinical Utilisation of Respiratory Elastance (CURE) Trial
-Optimising PEEP in mechanically ventilated patients

Lay title:

Optimising PEEP during mechanical ventilation

Co-ordinating investigator:

Assoc Prof. Geoffrey M Shaw

Participant's name:

English	I wish to have an interpreter	Yes	No
Deaf	I wish to have a NZ sign language interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero	Ae	Kao
Cook Island Māori	Ka inangaro au i tetahi tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Sāmoan	Ou te mana'o ia i ai se fa'amatala upu	loe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	loe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

I have read and I understand the information sheet dated 4th September 2014 for people taking part in the randomised control trial designed to optimise PEEP in mechanically ventilated patients in ICU. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use family/whanau support or a friend to help me ask questions and understand the study.

I believe that _____ (participant's name) would have chosen and consented to participate in this study if he/she had been able to understand the information that I have received and understood.

I understand that taking part in this study is voluntary and that my relative/friend may withdraw from the study at any time if I or he/she wishes. This will not affect his/her continuing health care.

I understand that his/her participation in this study is confidential and that no material which could identify him/her will be used in any reports on this study.

I understand that the study will be stopped if it should appear to be harmful.

I understand the compensation provisions for this study.

I know whom to contact if anything occurs that might make my relative/friend consider withdrawing from the study.

I know whom to contact if I have any questions about the study.

This study has been given ethical approval by the Southern Health and Disability Ethics Committee. This means that the Committee may check at any time that the study is following appropriate ethical procedures.

Date:

/ / 201__

Signature:

Printed name:

Relationship to participant:

Address for results:

Full names of researchers:

Assoc Prof Geoffrey M Shaw
Dist Prof J Geoffrey Chase
Dr Yeong Shiong Chiew

Contact phone number for researchers:

(03) 364 1077

Project explained by:

ICU position or project role:

Signature:

Date:

/ / 201__

STATEMENT BY CO-ORDINATING INVESTIGATOR

I, Assoc Prof. Geoffrey M Shaw declare that this study is in the potential health interest of the group of patients of which _____ (*name of participant*) is a member and that participation in this study is not adverse to _____ (*name of participant*)'s interests.

I confirm that if the participant becomes competent to make an informed choice and give an informed consent, full information will be given to him/her as soon as possible, and his/her participation will be explained. If the participant makes an informed choice to continue in the study, written consent will be requested and if the participant does not wish to continue in the study, he/she will be withdrawn.

Signed:

Date:

(Co-ordinating Investigator)

(If applicable at a later stage)

I _____ (*participant*) have read the information sheet for participants in the study "*Clinical Utilisation of Respiratory Elastance (CURE) Study: Optimising PEEP in mechanically ventilated patients*". I have had the opportunity to ask questions so that I can be fully informed about this study agree to continue taking part in it.

I wish to receive a copy of my results.

☐

Yes

☐

No

I wish to receive copies of scientific publications from this study.

☐

Yes

☐

No

I agree to my GP being informed of my participation in this study.

☐

Yes

☐

No

Signed:

Date:

(Participant)

Information Sheet for Participants

Clinical Utilisation of Respiratory Elastance: the 'CURE' Study -Optimising PEEP in mechanically ventilated patients.

Co-ordinating Investigator	
Assoc Professor Geoffrey M Shaw Intensivist Department of Intensive Care Medicine Christchurch Hospital Phone: (03) 364 1077	
Co Investigators	
Dist. Prof J. Geoffrey Chase Professor at University of Canterbury Department of Mechanical Engineering University of Canterbury Phone: (03) 364 2987 ext 7224	Dr. Yeong Shiong Chiew Post Doctoral Fellow Department of Mechanical Engineering University of Canterbury Phone: (03) 364 2987

Participation

You were recently looked after in the Intensive Care Unit (ICU) because at that time your lungs were not working properly, so a ventilator was used to help you breathe. We are currently conducting a research study looking at safer ways to ventilate patients who have sick lungs.

The study is called a Clinical Utilisation of Respiratory Elastance (CURE) randomised control trial (RCT). A RCT involves a random allocation of yourself into one of two groups. You have either A) received standard treatment or B) received standard treatment with the aid to potentially improve your recovery. In either treatment, breathing data was recorded using a bedside computer with doctors choosing the safest mechanical ventilator setting. You will not know which random allocation you have been assigned whether it be A) or B).

It was not possible to ask you to participate in this study because you were too unwell and had been given sedation. However, we discussed this study with your family, and / or close friends, and / or whanau, who believed you would have agreed to participate if you had been able to provide consent at that time. The information below was considered by your family, close friends, or whanau, when they agreed to the participation in the study. We would like you to consider the same information agreeing to continue participation in the study. You do not have to take part in this study, and if you do not wish to take part, your future healthcare will not be affected.

It is important that you read and understand this information sheet. It describes the purpose, procedures, and benefits of the study and your right to withdraw.

Introduction

Intensive care doctors and nurses use ventilators to support a person's breathing in intensive care. Pneumonia, trauma, inflammation, or too much fluid in the lung stops it from working properly. When this happens the lung gets "stiff"; this makes breathing difficult. The lungs become stiffer because the injury or infection causes many of the air sacs, (alveoli) to collapse. This is known as Acute Respiratory Distress Sndrome (ARDS).

Some people with stiff lungs will need their breathing helped by a ventilator. However, the ventilator, keeping them alive, may make their lungs worse. High breathing volumes and/or pressures can damage stiff lungs. Unfortunately, the lung can't be rested and immobilised like a broken bone, so it is very important we ensure the ventilator does not cause more lung injury.

The stiffness of the lung may be reduced by carefully inflating the collapsed regions using a "recruitment manoeuvre" (RM). During a RM the lung is gently inflated over a number of breaths by not allowing the lung to completely breathe out. ICU doctors and nurses do this by increasing the Positive End Expiratory Pressure (PEEP) setting on the ventilator.

Our research aims to find out if people on mechanical ventilation in intensive care are helped by keeping their lung stiffness as low as possible through use of RMs and optimal levels of PEEP. In this way, we hope to minimise the damage done to the lung by the ventilator.

Selection

Your relative or friend has been asked to consider your participation in this study because you were ventilated and had a diagnosis of ARDS.

The Study

You were ventilated using settings chosen by the ICU doctors. Currently, doctors have no standard way of selecting PEEP, so they use their best guess. Too much PEEP over stretches the lung, while too little PEEP causes collapse. Too much, or too little, PEEP makes the lung stiffer. Every person's lung is different, and his or her lung condition may also change during their stay in ICU. Therefore, choosing the level of PEEP can be quite tricky, and might not always be right.

The lung's stiffness, or *elastance*, is measured directly at the bedside using a laptop computer. To help doctors decide the best settings, the PEEP will be changed upwards and then downwards. For each of the changes, their responses will be recorded.

You were allocated to either A) a standard ventilation treatment or B) a ventilation treatment using a computerised method, which selects PEEP according to how stiff their lungs are. A randomised trial means every person, who is eligible to take part in this study, has an equal chance of receiving either treatment. This means the results of this research are not influenced by the ICU doctors or nurses.

If you were in group A) you received usual ventilation care by ICU doctors and nurses. A computer recorded the information from the ventilator, but this did not influence your care.

If you were in group B) **a computer recorded the information from the ventilator and recommend the best PEEP setting on the ventilator.** The doctors used the PEEP calculated by the computer setting if they thought it would help your care. Your lung "stiffness" would have changed over time, so we will also checked your lung stiffness at regular intervals and each time you were turned in bed. The PEEP settings were adjusted as necessary.

Risks

There was a risk that the PEEP setting suggested by the computer model might not have been the best for your lungs. This risk was minimised by asking the doctor if they agree with the PEEP level suggested by the computer. If the ICU doctor was not satisfied with the computer's suggestion, they chose another PEEP, which they considered more appropriate. The computer could not adjust the PEEP by itself; an ICU staff member made these changes manually.

Possible Benefits

You may or may not have experience any benefits from taking part in this study. However, frequent attention was paid to the way you were ventilated, and the settings were adjusted more than usual, which might have allowed you to get faster better.

If our method is found to help ICU patients in Christchurch, this method could be become more widely adopted, and significantly change the experiences of patients receiving ventilation in ICUs all over the world.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you will be eligible to apply for accident compensation (ACC) within its limitations. If you have any questions about ACC, please feel free to ask the researcher for more information before you agree to take part in this trial.

ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2001 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

Stopping participation in this study

You are free to withdraw from this study, without having to give a reason, and this will not affect your continuing health care.

The ICU doctors might have stopped your participation in this study, at any time and for any reason. If this did happen, it might have been because your condition had changed, or because of technical problems relating to the equipment. In any case, we will tell you why.

Research Funding

This research is supported by the Health Research Council of New Zealand (HRC).

Confidentiality

If you agree to take part in this study, the information obtained will be shared amongst investigators within the Department of Intensive Care, and the Centre for Bioengineering, University of Canterbury. However, no sensitive information will be collected, discussed or shared even amongst the research team. Only information that is directly relevant to this study will be used.

On any documents relating to the study, only a study code, or local ICU admission number, will identify them. Your National Health Information (NHI) number or any personal details that could identify you will not be used. You will not be personally identified in any reports on this study. Your medical information will be processed on a computer and held for up to 20 years. Study information will be kept secure. De-identified information may be shared amongst other researchers in this field. Results of this study will be presented at conferences and submitted for publication in medical and bioengineering journals. By signing the accompanying form, you agree to participate in this research, the record review, information storage, and data transfer described above.

Contact Details

For more information about this study, please feel free to contact the people below. You are also welcome to discuss this study with any of the Intensive Care doctors. You may telephone the ICU staff at any time (day or night) if you have any important concerns.

Health and Disability Services Consumer Advocate:

If you, your relative, or friend have any queries or concerns regarding their rights as a participant in this study, they may wish to contact a Health and Disability Services Consumer Advocate:

Telephone (03) 377 7501 or 0800 377 766 outside Christchurch.

Maori Health Support:

Eru Waiti

Maori Health Services

Canterbury District Health Board

Telephone: (03) 364 0640 Ext 88797; Mobile: 027 382 6587

Email: Eru.Waiti@cdhb.health.nz

Intensive Care:

Assoc Prof Geoffrey M Shaw (Co-ordinating Investigator)

Department of Intensive Care

Christchurch Hospital

Private Bag 4710

Christchurch 8011

Email: Geoff.Shaw@cdhb.health.nz

Intensive Care Unit Reception:

Direct Dial: (03) 364 1077

This study has received ethical approval from the Southern Health and Disability Ethics Committee.

Thank you for considering participation in this study.



Geoff Shaw,

Co-ordinating Investigator

Appendix E: CURE-RCT Clinical Protocol Flow Diagram

